BASIC, CLINICAL AND SPECIAL ISSUES IN MEDICINE

EDITORS
Assist. Prof. Dr. Yeliz KAŞKO ARICI
Assist. Prof. Dr. Tuba GUL

İKSAD
Publishing House

BASIC, CLINICAL AND SPECIAL ISSUES IN MEDICINE

EDITORS

Assist. Prof. Dr. Yeliz KAŞKO ARICI
Assist. Prof. Dr. Tuba GUL

AUTHORS

Assoc. Prof. Dr. Atakan SAVRUN
Assoc. Prof. Dr. Deha Denizhan KESKİN
Assoc. Prof. Dr. Emre GÖKÇEN
Asst. Prof. Dr. Gonca GULBAY
Assoc. Prof. Dr. Harun GUNES
Assoc. Prof. Dr. İbrahim ÇALTEKİN
Assoc. Prof. Dr. Seda KESKİN
Asst. Prof. Dr. Ali AYGUN
Asst. Prof. Dr. Halil YILMAZ
Asst. Prof. Dr. Nihan BOZKURT
Asst. Prof. Dr. Şeyda Tuba SAVRUN
Asst. Prof. Dr. Sumeyya Deniz AYBEK
Asst. Prof. Dr. Şükran KAYGISIZ
Asst. Prof. Dr. Tuba GÜL
Res. Asst. Dr. Deniz TANRIVERDİ
Res. Asst. Dr. Hamza Enes GÜÇLÜ
Dr. Kubra SAHIN
Dr. Zuhal KOÇ APAYDIN
Dr. Neslişah GÜR KURÇALOĞLU
Dr. Mustafa Said ACAR
Dr. Esma BULUT
Dr. İsmail Kıvanç CEBECİOĞLU
M.D. Adem KÖKSAL
M.D. İhya OBRUKÇU
M.D. Mesut TOMAKİN
M.D. Seyma UNUVAR GOK
M.D. Kaan Turan KARAKAYA
M.D. Zeynep UNUS YILMAZ
Res. Asst. Ali HÜSEYİNOĞLU
Res. Asst. Begüm Naz MEYDAN
Res. Asst. Elif Yaren KURUL
Res. Asst. Elif KELEŞ TAYFUR
Res. Asst. Elif UĞUR
Res. Asst. Fatmanur ÇAVDAROĞLU
Res. Asst. Furkan ELMAS
Res. Asst. Furkan KARA
Res. Asst. Meryem BALCI
Res. Asst. Sadegul SAVKIN
Res. Asst. Okay ALPTEKİN
Res. Asst. İshak ÖZKAY
Res. Asst. Yusuf Burak KALAFAT
PhD. Kubra SAHIN
Phd. MD. Aydın Sinan APAYDIN
Phd. MD. Aydın Sinan APAYDIN
MSc. Suheyla Pınar CELIK
Emergency Medicine Physician Rahime Şahin TURAN

İKSAD Publishing House

(The Licence Number of Publicator: 2014/31220)
TURKEY TR: +90 342 606 06 75
USA: +1 631 685 0 853
E mail: iksadyayinevi@gmail.com
www.iksadyayinevi.com

It is responsibility of the author to abide by the publishing ethics rules.
Iksad Publications – 2022©

ISBN: 978-625-6955-78-3
Cover Design: İbrahim KAYA
December / 2022
Ankara / Turkey
Size = 16x24 cm

CONTENTS

PREFACE

Since human beings can understand the value of being healthy only when they are sick, the importance of health professionals and medical education is understood more clearly every day due to the rapidly increasing number of patients and the diversity of diseases. The intertwined composition of basic and clinical medical sciences is the main element that forms the infrastructure of health sciences and medical education. In the field of health, the number of scientific publications and scientific organizations organized on academic platforms that reveal the importance and necessity of multidisciplinary and interdisciplinary practices in all respects, and thus more efficient results can be obtained has been increasing recently. With the advancement of technology, different perspectives, innovative research, and treatment methods, and even new branches of science are developing in the field of health sciences. Today, although a well-equipped and harmonious team, a long time, intensive effort, socio-economic opportunities, and a working process to be carried out with perseverance, principles, and patience are necessary for these developments, it has become so easy to access all these scientific publications and academic resources as a result of the digital age. The scientific texts in this book are the product of the devoted and meticulous work of academicians in different branches and each of whom is an expert in their field. Our aim in writing this work is to present different topics in basic and clinical sciences in the field of medicine, without subject limitation, from a multidisciplinary and interdisciplinary perspective, in a comprehensive, clear, and understandable language without boring the reader, and to ensure that you benefit from it as a source of information and reference for students, academicians, everyone interested in health sciences and you, our valued readers. Each chapter in this book has been blindly refereed and the academic and legal responsibility belongs to the relevant department authors.

We would like to express our sincere gratitude to all our authors who have contributed to our carefully prepared book and to our valuable readers, for their contributions and support. We hope to be able to reunite with our new works in the near future and wish you pleasant readings.

Asst. Prof. Dr. Yeliz KAŞKO ARICI [1]
Asst. Prof. Dr. Tuba GÜL[2]

[1] Ordu University, Faculty of Medicine, Department of Biostatistics and Medical Informatics, Ordu, Turkiye. ykaskoarici@odu.edu.tr, Orcid ID: 0000-0001-6820-0381
[2] Ordu University, Faculty of Medicine, Department of Neurology, Ordu, Turkiye. tglyzc@hotmail.com, Orcid ID: 0000-0001-6003-5975

CHAPTER 1

MOLECULAR BIOLOGY OF CHRONIC MYELOID LEUKEMIA

Assist. Prof. Dr. Gonca GULBAY[1]

[1] Ordu University, Faculty of Medicine, Department of Medical Biology, Ordu, Turkey. goncagulbay@odu.edu.tr, Orcid ID: 0000-0001-5201-6352

INTRODUCTION

Cancer is caused by the accumulation of DNA damage in cells, resulting in changes in critical genes that control cell division, differentiation and survival. Cancers; It is collected in three main groups as carcinomas, sarcomas, hematopoietic and lymphoid malignancies. Leukemia and lymphomas account for 7% of human cancers (Cooper and Hausman, 2006). Chronic myeloid leukemia (CML) accounts for 15-20% of all leukemia cases (Cotta and Ramos, 2007).

1. HISTORY OF CHRONIC MYELOID LEUKEMIA

The first definition of chronic myeloid leukemia (CML) as leukemia dates back to 1845. John Bennett and Rudolf Virchow independently of each other published reports of patients with splenomegaly, liver enlargement, and leukocytosis. However, Virchow was the first to use the term "Leukämie" meaning "white blood". Before long, Ernst Neumann defined leukemia as a disease originating from the bone marrow. In 1960, Peter Nowell and David Hungerford first demonstrated the existence of a link between chromosomes and cancer by reporting that an abnormal chromosome structure was identified in patients with chronic granulocytic leukemia using a method similar to karyotyping in mitotic cells in Philadelphia, USA. This chromosome became known as “Philadelphia (Ph) chromosome” after the name of the city where it was located. In 1973, Janet Rowley used staining methods such as chromosomal quinacrine fluorescence and giemsa banding and demonstrated for the first time a chromosomal translocation causing cancer by determining that this new chromosomal structure occurred as a result of reciprocal translocation between chromosomes 9 and 22 [t(9;22)] (Minciacchi, Kumar and Krause, 2021).

2. MOLECULAR MECHANISM OF CHRONIC MYELOID LEUKEMIA

CML is a clonal disorder characterized by increased proliferation and decreased apoptosis of a pluripotent stem cell in myeloid progenitor cells (Bennour, Saad and Sennana, 2016). This disease is characterized by a reciprocal t(9;22) chromosomal translocation resulting in the formation of the Philadelphia (Ph) chromosome containing the *BCR-ABL1* gene. Ph chromosome (Ph+) has been detected in 95% of patients diagnosed with CML (Corbin et al, 2011).

The most important factor causing CML is the presence of the Ph chromosome, which is formed as a result of reciprocal translocation between the 9th and 22nd chromosomes (Branford et al, 2003). Ph chromosome [t(9;22) (q34;q11)] is formed as a result of reciprocal translocation [t(9;22)] between the long arms of chromosomes 9 and 22, which causes the *BCR* and *ABL1* genes to come together. This newly formed chromosome gives rise to a

chimeric fusion gene. This gene is the *BCR-ABL1* gene (Chereda and Melo, 2015; Burslem et al, 2019).

CML is characterized by three distinct clinical stages. According to the World Health Organization (Arber et al, 2016), these phases are characterized as chronic, accelerated, and blast, and they are distinguished as follows :

1. Chronic Phase: Patients are often diagnosed in this phase. There is an increase in maturing myeloid cells. At this stage, the number of leukocytes in the bone marrow or blood is considerably increased. Symptoms are milder than other phases. The molecular abnormality of BCR-ABL1 fusion must be demonstrated to confirm the diagnosis (Haznedaroğlu, Kuzu and Ilhan, 2020)
2. Accelerated Phase: The percentage of blasts in peripheral blood or bone marrow ranges from 10 to 19 percent. The level of basophilia in peripheral blood is at least 20%. In addition, conditions such as splenomegaly, leukocytosis, and thrombocytopenia or thrombocytosis that do not respond to treatment begin to manifest during this phase. New chromosomal abnormalities that were not identified in the chronic phase arise. In the bone marrow, megakaryocytic proliferation is found alongside collagen or reticulin fibrosis and/or severe granulocytic dysplasia.
3. Blastic Phase: In this phase, which is fatal if untreated, the blast rate in the peripheral blood or bone marrow exceeds 20%. Extramedullary tissues exhibit blast growth, and large blast foci or clusters are found in the bone marrow (Haznedaroğlu, Kuzu and Ilhan, 2020). Erythrocyte and platelet count decreases (Golemovic et al, 2005). The life expectancy of patients at this stage is considerably shortened and t(9;22) chromosome is observed in peripheral blood or bone marrow in more than 80%. In addition, trisomy 8, 17 and 19 anomalies also accompany t(9;22) translocation.

Peripheral blood and bone marrow samples are used in the molecular diagnosis of CML. Using karyotype analysis, fluorescence insitu hybridization (FISH) and polymerase chain reaction (PCR) methods, the fusion gene t(9;22) and its expression are determined (Jovanovski et al, 2020).

2.1 ABL1 Gene and Protein

The *ABL* gene is a human homologue of the Abelson Murine Leukemia Virus (v-ABL) oncogene (Minciacchi, Kumar and Kraus, 2021). The *ABL* gene is localized in region 34.1 (9q34) of chromosome 9. The *ABL* gene has 11 exons. The *ABL1* gene encodes a 145 kDa protein. This protein is a nonreceptor kinase. It is responsible for the regulation of cell growth, DNA repair, adhesion, programmed cell death and signal transduction (Mendes, Rana, Datoguia, Hamerschlak and Brumatti, 2022).

Exon 1 undergoes alternative splicing. As a result of alternative splicing, two isoforms of ABL proteins (1a and 1b) are formed (Zhou, Medeiros and Hu, 2018). Separate (6 kb and 7 kb) messenger RNA (mRNA) is formed by transcription of the exon. These two mRNAs encode different proteins. The N-terminal ends of these proteins differ. These isoform proteins are called ABL (ABL1) and Arg (ABL2) (Wang, 2014; Gu, Ryu and Pendergast, 2009).

The N-terminal end of the ABL1 protein has the SRC homology region (SH1, SH2 and SH3). SH1 is the tyrosine kinase domain. SH2 and SH3 are attachment points. ABL1 contains a proline-rich sequence (PxxP). At its C-terminal end are the nuclear localization (NLS) and nuclear-exit signaling (NES) regions. These motifs are not found in ABL2 (Arg). Apart from these regions, DNA binding and G-actin (GBD) and F-actin (FBD) binding motifs, which are responsible for the binding of nuclear ABL to actin filaments in chromatin and cytoplasm, are also found in protein structure. Apart from these, Ataxia teleangiectasia mutated (Atm), Cdc2, Protein kinase C (PKC) and Tyrosine 393 (Y393) are phosphorylation sites (Srinivasan, Kaetzel and Plattner, 2009).

The breakpoints of the *ABL1* gene are concentrated at the 5' terminal end. These breakpoints can occur at multiple points in the first exon. In *ABL1*, breakpoints are located in the intron, between exon 1b and 1a, or in the intron between exon 1a and 2. *ABL1* is always spliced with two alternatives (1a and 1b) of the first exon, regardless of the breakpoints. Common exons (2-11) of *ABL1* are then assembled into different exon sets of BCR (Figure) (Zhou, Medeiros and Hu, 2018).

2.2 BCR Gene and Protein

The *BCR* (Breakpoint Cluster Region) gene is located in the q11 (22q11) region of chromosome 22. The *BCR* gene has 23 exons. The *BCR* gene encodes a 160 kDa protein. This protein is a serine-threonine kinase encoded by the first exon at the amino end of the BCR (Zhou, Medeiros and Hu, 2018; Kurzrock, Kantarjian, Drucer and Talpaz, 2003). The BCR protein carries the coiled-coil domain, which shows serine/threonine kinase activity. This domain provides autophosphorylation of BCR and phosphorylation of BAP-1 (BCR-Associated Protein-1) (De Braekeleer et al, 2011). Rho-GEF (Guanine Exchange Factor) domain; It acts as GEF for Rho proteins. It performs kinase activation in G proteins by converting guanidine triphosphate to diphosphate (GTP→GDP) (Peng et al, 2021). The C-terminal end of the BCR carries the GTPase-activating protein (GAP) domain. The GAP domain causes inhibition of tyrosine kinase activity. There are three breakpoint cluster regions in the BCR. These regions are major (M-BCR), minor (m-BCR) and micro (μ-BCR) regions corresponding to three fusion proteins named P210, P190 and P230, respectively (Zhou, Medeiros and Hu, 2018).

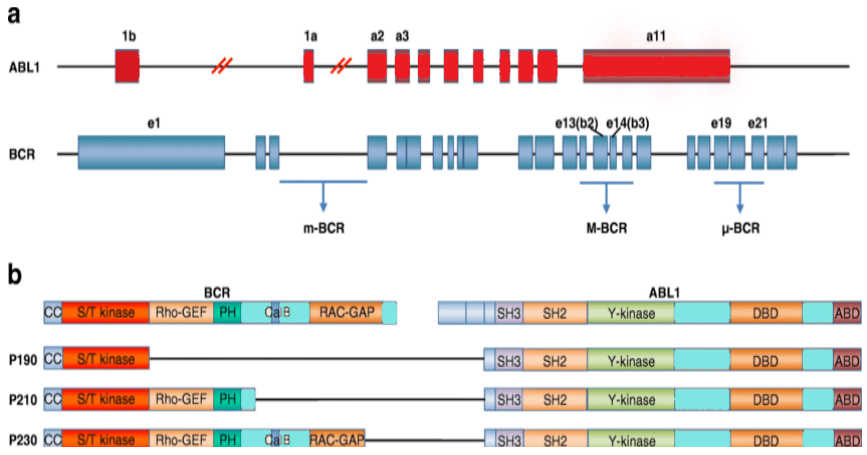


Figure. *BCR* and *ABL1* gene structures and structure of BCR-ABL1 fusion proteins (Zhou, Medeiros and Hu, 2018).

a. Gene structure and breakpoints (parallel slashes) of *BCR* and *ABL1*.
b. Major domains of BCR-ABL1 fusion proteins.

2.3 BCR-ABL1 Fusion Gene and Protein

The *BCR-ABL1* fusion gene is formed by taking the 5' end from BCR and the 3' end from ABL1. All three of the BCR-ABL1 fusion proteins (P210, P190 and P230) contain common ABL1 domains (Score et al, 2010). Depending on the BCR breakpoints, fusion proteins contain some or all of the BCR domains. Different BCR-ABL1 proteins have a clear association with different disease phenotypes (Zhou, Medeiros and Hu, 2018).

1. The P210 form is found in approximately 98% of CML, while it has been reported in up to 20% of Ph+ B-lymphoblastic leukemia/lymphoma (B-ALL) (Goh et al, 2006; Arun et al, 2017). Fracture occurs in the major-BCR (M-BCR) region. The resulting hybrid transcript weighs 210 kDa. It often occurs in the intron after exon 13 or exon 14. The e13a2 (b2a2) and e14a2 (b3a2) transcript subtypes encoding p210 occur in approximately 98% of CML cases (Ren, 2005; Ahmed and Van Etten, 2013; Cilloni and Saglio, 2012). The incidence of other minor transcripts is approximately 2% (Goh et al, 2006; Arun et al, 2017).
2. The P190 BCR-ABL1 form is found in more than 80% of Ph+ B-ALL. However, it is rarely observed in CML (Gong et al, 2017). The fracture occurs after the 1st exon. The resulting hybrid transcript weighs 190 kDa.

3. The rare transcript P230 (e19a2) has been identified in a small proportion of CML patients. Occurs after exon 19. The resulting hybrid transcript weighs 230 kDa (Zhou, Medeiros and Hu, 2018).

Due to their low frequency, the clinical significance of other rare transcripts is not clear (Zhou, Medeiros and Hu, 2018). The 210 kDa BCR-ABL1 protein observed in CML contains more than ten protein domains. BCR-ABL1 protects the Serine/Threonine kinase, Rho/GEF and dimerization (coiled-coil) domains from the BCR. Proline-rich (PxxP) DNA and actin-binding domains from ABL1 are coupled to SH by nuclear localization and entry signals. The SH1 tyrosine kinase domain is the most studied BCR-ABL1 domain because of its inherent role in CML pathogenesis (Chu, Li, Singh and Bhatia, 2007; Zhang et al, 2001).

3.MALIGN TRANSFORMATION MECHANISMS

Loss of the N terminus of the *BCR* gene during the formation of the *BCR-ABL1* fusion gene results in increased tyrosine kinase activity in the chimeric protein. This increase in activity leads to abnormal activation of cell signaling pathways and a transition to a cellular environment that supports leukemia. The activation of this pathway has been associated with inhibition of programmed cell death, alteration of proliferation and cell adhesion properties, and mitogenic activation (Chereda and Melo, 2015).

3.1 Change of Adhesion Properties

CML progenitor cells escape the mechanism that negatively regulates cell division. Studies have shown that β-integrins play an important role in the interaction between the stroma and progenitor cells. An adhesion-inhibiting variant of β1-integrin has been detected in CML cells. This variant is not expressed in normal progenitor cells (De Moraes et al, 2012).

3.2 Inhibition of Apoptosis

Presence of DNA damage in cell induces apoptosis pathways. Studies have shown that CML cells are resistant to apoptosis. However, the mechanisms of inhibition of apoptosis have not been fully elucidated. However, it is thought that the chimeric protein prevents the release of cytochrome c from mitochondria by providing caspase activation with the effect of Bcl-2 family members. In addition, there are opinions that phosphorylation of Bad, a pro-apoptotic protein, has a role in apoptosis inhibition (Hamad, Sahli, El Sabban, Mouteirik and Nasr, 2013).

3.3 Mitogenic activation

3.3.1 Ras/Raf/Mek/Erk Pathway

The RAS/RAF/MEK/ERK pathway is a central signal transduction pathway that transmits signals from cell surface receptors to nuclear transcription factors. Ras are proteins with GTPase activity. Cell proliferation, apoptosis, cellular events such as migration and differentiation they take part in the control. As a result of stimuli from outside the cell, GTP-binding Ras activates Raf. The cascade continues with MEK and ERK activations, respectively (Kang et al, 2016; Mizuchi et al, 2005).

In animal model studies, disruption of Ras signaling has been shown to impair the development of BCR-ABL1-induced CML-like disease in mice (Mendes, Rana, Datoguia, Hamerschlak and Brumatti, 2022; Baum and Ren, 2008). In BCR-ABL1 positive leukemia cells, activation of the RAS/RAF/MEK/ERK pathway results in uncontrolled proliferation (Mizuchi et al, 2005). BCR-ABL1 activates Ras via Grb2/Gab2 phosphorylation to promote cell growth (Chu, Li, Singh and Bhatia, 2007).

3.3.2 PI3K/AKT/mTOR Pathway

PI3-Kinase (Phosphatidylinositol 3-kinase proteins) transduce extracellular signals to modulate transcription factor activation and programming promoting cell growth/survival and inhibition of cell death. BCR/ABL1 positive cells require PI3-Kinase activity to divide. Activation of this pathway activates the Akt cascade, a serine-threonine kinase. Akt phosphorylates numerous proteins that regulate apoptosis. This kinase is effective in the anti-apoptotic pathway (Zhao et al, 2006). There are studies suggesting that PI3K signaling arrest may inhibit BCR-ABL1 oncogenesis and kill primary CML cells. Another consequence of PI3K activation is the stimulation of the mTOR pathway, which is responsible for controlling protein synthesis, cell growth/size and autophagy (Klejman, Rushen, Morrione, Slupianek, and Skorski, 2002).

3.3.3 Jak/STAT Pathway

Signaling from the JAK/STAT pathway is commonly increased in leukemias (Chereda and Melo, 2015). STAT (signal transducer and activator of transcription) proteins are transcription factors activated by the Janus kinase (JAK) cell receptor (Hennighausen and Robinson, 2008). CML cell models have shown that BCR-ABL1 kinase activity directly enhances JAK2/STAT activation to promote cell growth/survival (Warsch, Walz and Sexl, 2013).

CONCLUSION

CML is one of the most commonly diagnosed forms of leukemia. Recent advances in understanding the molecular mechanisms involved in the pathogenesis of this disease have led to new diagnostic and therapeutic approaches. While CML was a disease diagnosed on morphologic grounds, the

high degree of association between BCR-ABL1 and CML has transformed CML into a disease form that can be diagnosed in the presence of relevant cytogenetic or molecular data.

REFERENCES

Ahmed, W., Etten, V,R,A. (2013). Alternative approaches to eradicating the malignant clone in chronic myeloid leukemia: tyrosine-kinase inhibitor combinations and beyond. *Hematology Am Soc Hematol Educ Program*;189-200.

Arber, D,A., Orazi, A., Hasserjian, R., Thiele, J., Borowitz, M.J., Le Beau, M,M., Bloomfield, C,D., Cazzola, M., Vardiman, J,W. (2016). The Updated Who Classification of Hematological Malıgnancies. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*; 127 (20).

Arun, A. K., Senthamizhselvi, A., Mani, S., Vinodhini, K., Janet, N. B., Lakshmi, K. M., Abraham, A., George, B., Srivastava, A., Srivastava, V. M., Mathews, V., Balasubramanian, P. (2017). Frequency of rare BCR-ABL1 fusion transcripts in chronic myeloid leukemia patients. *Int J Lab Hematol*; 39(3), 235-242.

Baum, K,J., Ren, R. (2008). Effect of Ras inhibition in hematopoiesis and BCR/ABL leukemogenesis. *J Hematol Oncol*; 1:5

Bennour, A., Saad, A., Sennana, H. (2016). Chronic myeloid leukemia: Relevance of cytogenetic and molecular assays. *Crit Rev Oncol Hematol*; 97: 263-274

Branford, S., Rudzki, Z., Walsh, S., Parkinson, I., Grigg, A., Szer, J., Taylor, K., Herrmann, R., Seymour, J. F., Arthur, C., Joske, D., Lynch, K., Hughes, T. (2003). Detection of BCR-ABL mutations in patients with CML treated with imatinib is virtually always accompanied by clinical resistance, and mutations in the ATP phosphate-binding loop (P-loop) are associated with a poor prognosis. *Blood*, 102(1), 276-283.

Burslem, G. M., Schultz, A. R., Bondeson, D. P., Eide, C. A., Savage Stevens, S. L., Druker, B. J., Crews, C. M. (2019). Targeting BCR-ABL1 in Chronic Myeloid Leukemia by PROTAC-Mediated Targeted Protein Degradation. *Cancer Res*, 79(18), 4744–4753.

Chereda, B., Melo, J,V. (2015). Natural course and biology of CML. *Ann Hematol*; 94 (Suppl 2):107-121

Chu, S, Li, L, Singh, H., Bhatia, R. (2007). BCR-tyrosine 177 plays an essential role in Ras and Akt activation and in human hematopoietic progenitor transformation in chronic myelogenous leukemia. Cancer Res ; 67 (14): 7045-7053

Cilloni, D., Saglio, G. (2012). Molecular pathways: BCR-ABL. *Clin Cancer Res* ; 18 (4): 930-937

Cooper, M,G., Hausman, R,E. (2006). Hücre, Moleküler Yaklaşım, İzmit Tıp Kitap Evi, İzmir, 631-673

Corbin, A,S., Agarwal, A., Loriaux, M., Cortes, J., Deininger, M,W., Druker, B,J. (2011). Human chronic myeloid leukemia stem cells are insensitive to imatinib despite inhibition of BCR-ABL activity. *J Clin Invest* 2011; 121 (1): 396-409.

Cotta, C,V., Ramos, C,E,B. (2007). New insights into the pathobiology and treatment of chronic myelogenous leukemia. *Ann Diagn Pathol*;11(1):68-78

De Braekeleer, E., Douet-Guilbert, N., Rowe, D., Bown, N., Morel, F., Berthou, C., Férec, C., De Braekeleer, M. (2011). ABL1 fusion genes in hematological malignancies: a review. *Eur J Haematol*; 86(5), 361-371.

Goh, H,G., Hwang, J,Y., Kim, S,H., Lee, Y,H., Kim, Y,L., Kim, D,W. (2006). Comprehensive analysis of BCR-ABL transcript types in Korean CML patients using a newly developed multiplex RTPCR. *Transl Res* ; 148 (5): 249-256.

Golemovic, M., Verstovsek, S., Giles, F., Cortes, J., Manshouri, T., Manley, P. W., Mestan, J., Dugan, M., Alland, L., Griffin, J. D., Arlinghaus, R. B., Sun, T., Kantarjian, H., Beran, M. (2005). AMN107, a novel aminopyrimidine inhibitor of Bcr-Abl, has in vitro activity against imatinib-resistant chronic myeloid leukemia. *Clin Cancer Res*; 11(13), 4941-4947.

Gong, Z., Medeiros, L. J., Cortes, J. E., Zheng, L., Khoury, J. D., Wang, W., Tang, G., Loghavi, S., Luthra, R., Yang, W., Kantarjian, H. M., Hu, S. (2017). Clinical and prognostic significance of e1a2 BCR-ABL1 transcript subtype in chronic myeloid leukemia. *Blood Cancer J*; 7(7), e583.

Gu, J,J., Ryu, J,R., Pendergast, A,M. (2009). Abl Tyrosine Kinases in T-cell Signaling, *Immunol Rev*; 228(1): 170-183

Hamad, A., Sahli, Z., El Sabban, M., Mouteirik, M., Nasr, R. (2013). Emerging therapeutic strategies for targeting chronic myeloid leukemia stem cells. *Stem Cells Int*, 2013, 724360.

Haznedaroğlu, I,C., Kuzu, I., Ilhan, O. (2016). WHO 2016 Definition of Chronic Myeloid Leukemia and Tyrosine Kinase Inhibitors. *Turk J Hematol*; 37:42-4

Hennighausen, L., Robinson, G,W. (2008). Interpretation of cytokine signaling through the transcription factors STAT5A and STAT5B. *Genes Dev*; 22(6): 711-721

Jovanovski, A., Petiti, J., Giugliano, E., Gottardi, E,M., Saglio, G., Cilloni, D., Fava, C. (2020). Standardization of BCR-ABL1 p210 Monitoring: From Nested to Digital PCR. *Cancers;* 12; 3287.

Kang, Z. J., Liu, Y. F., Xu, L. Z., Long, Z. J., Huang, D., Yang, Y., Liu, B., Feng, J. X., Pan, Y. J., Yan, J. S., Liu, Q. (2016). The Philadelphia chromosome in leukemogenesis. *Chin J Cancer*; 35, 48.

Klejman, A., Rushen, L., Morrione, A., Slupianek, A., Skorski, T. (2002). Phosphatidylinositol-3 kinase inhibitors enhance the anti-leukemia effect of STI571. *Oncogene*, 21(38), 5868–5876.

Kurzrock, R., Kantarjian, H,M., Drucer, B,J., Talpaz, M. (2003). Philadelphia chromosome positive leukemias: from basic mechanisms to moleculer therapeutics. *Ann Intern Med* ;138:819-30

Mendes, G,P,A., Rana, A., Datoguia, T,S., Hamerschlak, N., Brumatti, G. (2022). BCR-ABL1 Tyrosine Kinase Complex Signaling Transduction: Challenges to Overcome Resistance in Chronic Myeloid Leukemia. *Pharmaceutics*; 14: 215.

Minciacchi, V,R., Kumar. R., Krause, D,S. (2021). Chronic Myeloid Leukemia: A Model Disease of the Past, Present and Future. *Cells*; 10: 117

Mizuchi, D., Kurosu, T., Kida, A., Jin, Z. H., Jin, A., Arai, A., Miura, O. (2005). BCR/ABL activates Rap1 and B-Raf to stimulate the MEK/Erk signaling pathway in hematopoietic cells. *Biochem Biophys Res Commun*, 326(3), 645–651.

Nestal de Moraes, G., Souza, P. S., Costas, F. C., Vasconcelos, F. C., Reis, F. R., Maia, R. C. (2012). The Interface between BCR-ABL-Dependent and -Independent Resistance Signaling Pathways in Chronic Myeloid Leukemia. *Leuk Res Treatment*; 671702.

Peng, Y., Huang, Z., Zhou, F., Wang, T., Mou, K., Feng, W. (2021). Effect of HSP90AB1 and CC domain interaction on Bcr-Abl protein cytoplasm localization and function in chronic myeloid leukemia cells. *Cell Commun Signal* : CCS, 19(1), 71.

Ren, R. (2005) Mechanisms of BCR-ABL in the pathogenesis of chronic myelogenous leukaemia. *Nat Rev Cancer* ;5(3):172-183.

Score, J., Calasanz, M,J., Ottman, O., Pane, F., Yeh, R,F., Simoes, M,A,S., Kreil, S., Ward, D., Curtis, C,H., Melo, J,V., Wiemels, J., Nadel, B., Cross, N,C., Grand, F,H. (2010). Analysis of genomic breakpoints in p190 and p210 BCR-ABL indicate distinct mechanisms of formation. *Leukemia;* 24(10): 1742-1750

Srinivasan, D., Kaetzel, D,M., Plattner, R. (2009). Reciprocal Regulation of Abl and Receptor Tyrosine Kinases. *Cell Signal* ; 21(7): 1143-1150

Wang, J,Y,J. (2014).The Capable ABL: What Is Its Biological Function? *Mol Cell Biol*; 34 (7); 1188 -1197.

Warsch, W., Walz, C., Sexl, V. (2013). JAK of all trades: JAK2-STAT5 as novel therapeutic targets in BCR-ABL1+ chronic myeloid leukemia. *Blood*; 122 (13): 2167-2175

Zhang, X., Subrahmanyam, R., Wong, R., Gross, A. W., Ren, R. (2001). The NH(2)-terminal coiled-coil domain and tyrosine 177 play important roles in induction of a myeloproliferative disease in mice by Bcr-Abl. *Mol Cell Biol*; 21(3), 840-853.

Zhao, J. J., Cheng, H., Jia, S., Wang, L., Gjoerup, O. V., Mikami, A., Roberts, T. M. (2006). The p110alpha isoform of PI3K is essential for proper growth factor signaling and oncogenic transformation. *Proc Natl Acad Sci U S A*; 103(44), 16296-16300.

Zhou, T., Medeiros, L,J.,Hu, S. (2018). Chronic Myeloid Leukemia: Beyond BCR-ABL1. *Curr Hematol Malig Rep*; 13: 435-445.

CHAPTER 2

OVERVIEW OF THE EFFECTS OF PHEROMONES ON SEXUAL BEHAVIOR

Dr. Öğr. Üyesi Şükran KAYGISIZ[1]
Dr. Öğr. Üyesi Tuba GÜL[2]

[1] Ordu Üniversitesi, Tıp Fakültesi, Nöroloji Ana Bilim Dalı, Ordu, Türkiye. skrnkygsz52@gmail.com Orcid ID: 0000-0001-9779-8239
[2] Ordu Üniversitesi, Tıp Fakültesi, Nöroloji Ana Bilim Dalı, Ordu, Türkiye. tglyzc@hotmail.com Orcid ID: 0000-0001-6003-5975

INTRODUCTION

The importance of odors in mammalian reproductive behavior and pheromones have been the subject of research for years. Many experimental researches carried out in recent years have revealed with scientific evidence that the pheromones that individuals have are not only effective in their partners, but also in all kinds of bodily activities related to the individual's own behavior, mental state and emotional state, and that the change in the pheromone content and chemical structure of the individual due to any reason is primarily effective within itself (Hattori, et al., 2016; Keverne, 2004; Nagalingham, 2014). We see that the studies on pheromones in recent years have been concentrated in agriculture, animal husbandry, behavioral science, paramedical treatment methods, sociology, food sector, aromatherapy, pharmacotherapy and many other fields of science. The exchange of pheromones with food intake first began to be the subject of research in the 1970s in terms of the effects of feeds on livestock. Many living species have taken part in studies (Thomas Palo and Robbins, 1991).

Neuroendocrine Mechanisms

Preputial glands are exocrine glands that are found in the foreskin folds of the reproductive organs for many mammals and are known to produce pheromones. In females, they are known by the name of Bartholin gland. In men, they are located on the inner surface of the foreskin and form secretion of a dark consistency called smegma. There are many studies showings that removing the preputial glands makes female rats much less attractive to sexually experienced male rats, with female rats showing that their whole body odor (e.g., vaginal secretions or urine) is more attractive to male rats than the odors of prepressive gland tissue. In a study, it was stated that the production of female preputial gland odor was associated with the endocrine status of animals, and that there was a temporal relationship between the production of sexual odors by the female preputial gland and the onset of receptivity. In a similar study in which sexually experienced male rats were used to test the whole-body and preputial gland odors of female rats, male rats showed a tendency to intact ones, rather than females whose preputial glands had been removed by a noticeable margin. Instead of the female rats whose ovaries were removed, they were seen to turn to those that were not removed. They especially

preferred female rats before estrus and during estrus. While the pre-gland odors of rats who took estradiol benzoate for 7 days but had their ovaries removed were attractive to male rats, no effect was seen when given progesterone. However, a single injection of progesterone, given 72 hours after a single injection of estradiol benzoate, not only made rats whose ovaries had been removed receptive, but also made their preputial gland odor attractive to male rats. In the results; that the preputial gland of the female rat is responsible for the odors that serve to attract sexually experienced male rats, that ovarian steroids, in addition to increasing receptivity in the female rat, also control the production of pheromones in her preputial glands that increase their sexual attractiveness, that there is no relationship between the size of the preputial glands and their ability to attract male rats, so the growth of the preputial gland and the production of sex attractive substances are not under the same hormonal control (Thody and Dijkstra, 1978).

It has been confirmed by studies that melanocyte-stimulating hormone (MSH) also stimulates the production of preputial gland odors, but there is not enough data on whether other pituitary hormones have a similar effect. It has been shown in studies that pituitary hormones stimulate the growth of the preputial glands, and when progesterone or testosterone is administered together with MSH, there is a marked increase in efficacy, increasing not only the size of the preputial gland, but also its lipogenic activity. Similar research by Tirindelli et al. showed that there was no relationship between the size of the preputial glands and the presence of sexual attractions, and that although progesterone had a role in increasing the weight of the preputial glands, it had no effect on the secretion of gland odors. In particular, the view that most of the mammalian pheromones identified so far are lipids has lost its validity, and traces of lipids, proteins, and some different chemical compounds have been found in the content of pheromones, which vary according to species. It has been proven that olfactory organs have different neuronal subsets to detect pheromones, certain types of receptors for converting pheromone binding into electrical signals, second messenger systems, and ion channels. Calcium channels have been shown to be important at this point (Tirindelli et al., 2009).

Neuroanatomıc And Neurophysıologıcal Mechanısms

It has been shown that the pheromone belonging to a male or female individual stimulates different brain regions in a partner of the opposite sex, in another living being of the same sex, and in the individual himself who produces the pheromone (Keverne, 2004).

In a meta-analysis study that examined data from several studies using functional brain imaging techniques to investigate the neuroanatomical correlations of sexual arousal, subjects were asked to monitor and control visual sexual stimuli. As a result of the examination, cortical activation sites in heterosexual men; lateral has been shown to be occipitotemporal, inferotemporal, parietal, orbitofrontal, medial prefrontal, insular, anterior cingulate and frontal premotor cortices. In addition, the amygdala, claustrum, hypothalamus, caudate nucleus, thalamus, cerebellum, and substantia nigra are also important subcortical regions. Visual sexual stimuli caused more pronounced activation in men in the amygdala and thalamus. During ejaculation, decreased activation was observed throughout the prefrontal cortex. (Stoléru, et al., 2012).

While pheromones facilitate reproductive behavior in adult males, they do not form the same pattern of behavior in pre-pubescent males. Released from MPOA in response to a receptive female or its scent, DA is a key component of the neural events underlying adult male rat sexual behavior. In an experimental study in which it was investigated whether there was increased dopaminergic activity in response to female pheromones in adult male hamster MPOA and whether there was a difference in processes in prepubertal males; Levels of the primary metabolite DA (DOPAC) in MPOA increased significantly in adults after 15 minutes of pheromone exposure, but not in prepubertal men. These data explain why neural processing of sexually relevant chemosensory stimuli matures during adolescence, that there is no DA response to female pheromones before puberty, and that pre-pubescent males are unable to demonstrate reproductive behavior. (Schulz, et al., 2003).

In a study examining male reproductive behavior in the Syrian hamster, it was shown that there are variables linked to both pheromones from the female and the presence of gonadal steroid hormones. Pheromones (FHVS) found in the vaginal secretions of female hamsters stimulated the approach of the male to the female, anogenital research behavior, and mounting. Applying T to

castrated male hamsters facilitated anogenital research, mount count, and intromissions in adults, but only anogenital research in prepubertal men. Exposure to FHVS has shown increased Fos immunoreactivity in both prepubertal and adult males in the posterior lower part of the medial nucleus of the amygdala (MeP) and the posteromedial lower part of the bed nucleus of the stria terminal (BNSTpm). T in adult hamsters has been shown to affect neural and behavioral responses to pheromone exposure differently in men and women. (Romeo, et al., 1998; Fiber and Swann, 1996).

Other Factors Affectıng Pheromones

It has been shown that there are changes in endogenous secretions as well as external secretions such as sweat and tears with the foods taken. In a study conducted at the Weizzmann Institute of Science in Israel, the tears of women who cried in front of a film were collected and their emotionally stable male partners were sniffed for a long time, and it was found that the result was statistically significant men's T level drop and sexual reluctance. (Mishor, et al., 2021).

When the loss of sexual activation and reproductive disorders of animals exposed to toxic pesticides were examined, it was shown that there were pheromonal changes in body secretions. The emergence of this change may require long-term exposure in some living things. In poultry and farm animals, which were also examined in terms of reproductive behavior, it was shown that feeds caused changes in pheromone synthesis/release, energy metabolism, reproductive behaviors, and even in the content of animal products. (G.K. Beauchamp Diet influences the attractiveness of urine in guinea pigs Nature, Lond, 263 (1976), pp. 587-588))

Changes in pheromones have been shown to reduce the behavior of acceptance, adoption, and desire in a general environment not only with their partners but also in their social lives. It has been stated that consuming medical agents, foods taken for herbal therapy, excessive caffeine, etc. stimulants are the underlying causes of pheromone change. In direct proportion to how long smoking lasted, changes in pheromones could be detected even years after quitting smoking. (Oleszkiewicz, et al., 2021).

In studies conducted on homosexual individuals, it has been shown that pheromones change their perception, sexual desire, sexual preference, and

behavior patterns as a result of disruptions in olfactory receptors and perception centers in the brain, as well as causes such as intrauterine deficiency gonadal hormone exposure and genetic predisposition (Luoto, 2021). While the brain areas activated in the pheromone effect, desire to eat, and eating behavior are stimulated for the opposite sexes, it has been demonstrated by both detailed experimental studies and electrophysiological and functional imaging methods that pheromones affect the social behavior, motivation, functionality and emotional transition areas in the individual himself. (Ihara, et al., 2013; Brennan,2004).

REFERENCES

Brennan, P.A. (2004). The nose knows who's who: chemosensory individuality and mate recognition in mice. Horm Behav. 46(3): 231-40. doi: 10.1016/j.yhbeh.2004.01.010.

Fiber, J.M., Swann, J.M. (1996). Testosterone differentially influences sex-specific pheromone-stimulated Fos expression in limbic regions of Syrian hamsters. Horm Behav. 30(4): 455-73. doi: 10.1006/hbeh.1996.0050.

Beauchamp, G.K. (1976). Diet influences the attractiveness of urine in guinea pigs Nature. 263: 587-588.

Hattori, T., Osakada, T., Matsumoto, A. et al. (2016). Self-exposure to the male pheromone ESP1 enhances male aggressiveness in mice. Current biology, 26(9): 1229-1234.

Ihara, S., Yoshikawa, K., & Touhara, K. (2013). Chemosensory signals and their receptors in the olfactory neural system. Neuroscience, 254: 45-60.

Keverne, E.B. (2004). Importance of olfactory and vomeronasal systems for male sexual function. Physiol Behav, 83(2): 177-87. doi: 10.1016/j.physbeh.2004.08.013.

Luoto, S. (2021). Did prosociality drive the evolution of homosexuality? Response to Barron (2020). Archives of Sexual Behavior, 50(7): 2777-2779.

Mishor, E., Amir, D., Weiss, T. et al. (2021). Sniffing the human body volatile hexadecimal blocks aggression in men but triggers aggression in women. Science advances, 7(47):eabg1530.

Nagalingham, K. (2014). Functional significance of male attractants of Bactrocera tryoni (DiptERα: Tephritidae) and underlying mechanisms (Doctoral dissertation, Queensland University of Technology) erişim tarihi: 20.12.2022, erişim linki: https://www.semanticscholar.org/paper/Functional-significance-of-male-attractants-of-and-Nagalingham/c622357ef03590800b317b8ec6b47814e244fca4

Oleszkiewicz, A., Suhle, P., Haehner, A., & Croy, I. (2021). Prior exposure to Hedione, a model of pheromone, does not affect female ratings of male facial attractiveness or likeability. Physiology & Behavior, 238:113458.

Thomas, Palo, R., Robbins, C. T. (1991). Plant Defenses Against Mammalian HERbivory, CRC Press Book.

Romeo, R.D, Parfitt, D.B, Richardson, H.N, Sisk, C.L. (1998). Pheromones elicit equivalent levels of Fos-immunoreactivity in prepubertal and adult male Syrian hamsters. Horm Behav. 34(1):48-55. doi: 10.1006/hbeh.1998.1463.

Schulz, K.M., Richardson, H.N., Romeo, R.D. (2003). Medial preoptic area dopaminergic responses to female pheromones develop during puberty in the male Syrian hamster. Brain Res. 988(1-2):139-45. doi: 10.1016/s0006-8993(03)03358-4.

Stoléru, S., Fonteille, V., Cornélis, C. et al. (2012). Functional neuroimaging studies of sexual arousal and orgasm in healthy men and women: a review and meta-analysis. Neurosci Biobehav Rev. 36(6):1481-509. doi: 10.1016/j.neubiorev.2012.03.006.

Thody, A. J., Dijkstra, H. (1978). Effect of ovarian steroids on preputial gland odours in the female rat. Journal of Endocrinology, 77(3):397-403.

Tirindelli, R., Dibattista, M., Pifferi, S., & Menini, A. (2009). From pheromones to behavior. Physiological reviews, 89(3):921-956.

CHAPTER 3

AN OVERVIEW OF CYTOSKELETON AND ACTIN CYTOSKELETON RELATED DISEASES

Dr. Kubra SAHIN[1]
Asst. Prof. Dr. Nihan BOZKURT[2]
Res. Asst. Sadegul SAVKIN[3]

[1]Tokat Gaziosmanpasa University, Faculty of Medicine, Department of Medical Biology, Tokat, Türkiye.
kubra944@hotmail.fr, ORCID ID: 0000-0001-9870-0176
[2]Tokat Gaziosmanpasa University, Faculty of Medicine, Department of Medical Biology, Tokat, Türkiye.
nihan.bozkurt@gop.edu.tr, ORCID ID: 0000-0002-2283-0828
[3]Tokat Gaziosmanpasa University, Faculty of Medicine, Department of Medical Biology, Tokat, Türkiye.
sadegul.savkin@gop.edu.tr, ORCID ID: 0000-0002-9284-9102

INTRODUCTION

The cytoskeleton is one of the complex structures that play a role in many biological processes such as forming cell shape, maintaining their integrity, moving, adhesion, endocytosis, intracellular transport, cell division, force transmission, and response to external forces (Hohmann & Dehghani, 2019; Pollard & Goldman, 2018). The cytoskeleton requires the combined function of numerous cytoplasmic proteins and organelles to perform these functions. In addition, the cytoskeleton is not a fixed structure, but a dynamic and rearrangeable structure containing polymers and motor proteins (Fletcher & Mullins, 2010). The polymers interact with motor proteins, stabilizers, and crosslinkers to form network complexes. These networks determine the shape and mechanics of the cell (Bartolák-Suki et al., 2017). The eukaryotic cytoskeleton is a complex structure containing three protein polymers and three motor protein families, while the prokaryotic cytoskeleton has a simpler structure that includes only protein polymers (Pollard & Goldman, 2018). Microtubules, intermediate filaments, and microfilaments are eukaryotic polymers, and motor proteins are myosin, kinesin, and dynein. Prokaryotes have protein polymers homologous to actin and tubulin, and some bacteria have intermediate filament polymers (Pollard & Goldman, 2018). However, many strands of the bacterial cytoskeleton, such as eukaryotic actin-based microfilaments and tubulin-based microtubules, lack motor proteins because they are intrinsically cytomotive (Wickstead & Gull, 2011). Both actin microfilaments and microtubules are highly dynamic cytoskeletal components involved in a variety of intracellular, cell-cell, and cell-substrate interactions. Coordinated movement of microtubules and actin filaments are required to maintain cell shape and structure. The intermediate filaments are physically associated with actin and microtubules through molecular motors and cytoskeletal linkers throughout the cytoplasm supporting the organization of the cytoskeletal network (Ilan, 2018).

In recent years, a lot of information has been learned about the structure, function, and relationship of the cytoskeleton (especially the actin cytoskeleton) to diseases. For example, changes in actin and actin regulatory proteins have been associated with many diseases such as immune deficiency, neurodegenerative diseases, cancer, muscle diseases, and autoimmune and autoinflammatory diseases. This information has made actin filaments potential therapeutic targets for various disorders (Wickramarachchi, Theofilopoulos & Kono, 2010; Lai & Wong, 2020).

We started this section by talking about the three main filament types and the proteins associated with these filaments. Later, we focused on actin cytoskeleton rearrangements. Finally, we discuss actin cytoskeleton-related diseases.

1. CYTOSKELETAL POLYMERS

1.1. Microfilaments (Actin Filaments)

Microfilaments made up of actin are one of the essential components of the eukaryotic cytoskeleton (Li & Wu, 2003). Actin is the amplest protein in the eukaryotic cell, constituting 10% of the total protein in all eukaryotic cells. It is the protein family that is the most conserved and participates in the most protein-protein interaction in the evolutionary process (Kim et al., 2022; Merino, Pospich & Raunser, 2020). The actin molecules can exist in two forms, monomers or polymers. Monomeric actin molecules are globular proteins called Globular actin (G-actin), weighing 42 kDa, and there are 3 (α-actin, ɣ-actin, and β-actin) isoforms with different functions, among which several amino acid differences are observed (Blaine & Dylewski, 2020; Melekoglu & Karahan, 2019). The α-Actin is generally associated with muscle tissues, while the β-actin is often related to polymerization or other cellular interactions in a lot of cell types (Melekoglu & Karahan, 2019). The G actin molecules can polymerize into polymeric proto-filaments called fibrous actin (F-actin) (Blaine & Dylewski, 2020). This polymerization can be induced by solutions enriched with Mg^{2+}, K^{+}, or Na^{+} ions (Melekoğlu & Karahan, 2019). Two actin proto-filaments that polymerize make helical turns of 36 nm to form an actin filament (Feher, 2017; Jiang et al., 2021; Li & Wu, 2003). Microfilaments are organized into filament bundles, forming a three-dimensional intracellular network (Crawford, Bioulac-Sage & Hytiroglou, 2018). The microfilaments are highly dynamic and asymmetrical structures with different polymerization and depolarization rates called barbed (+) and pointed (-). The barbed end is the part where polymerization is faster (10 times faster) as a result of the binding of the G-actin monomers bound to ATP, while the pointed end is the part where polymerization is slower (Merino et al., 2020).

The actin cytoskeleton along with motor proteins and other actin-related proteins is the primary force-generating mechanism in the cell. It can produce repulsive (protruding) and pulling (contraction) forces through the coordinated polymerization of multiple actin filaments. The microfilaments which are important for cell migration produce both pushing and pulling

forces, also they play a role in many processes, such as defining and modifying cell shape and cell surface mechanical properties, managing muscle contraction, cell migration, directing intracellular motility, cellular movement and morphogenesis of membrane organelles. Moreover, they provide cells to form adhesions with each other, other cells, and the extracellular matrix (Svitkina, 2018). The actin cytoskeleton forms actin-based structures such as lamellipodium, filopodium, stress fibers, actin cortex, and nuclear actin in order to perform these functions (Hohmann & Dehghani, 2019). Nuclear actin participates in the regulation of gene expression as a component of chromatin rearrangement complexes (Izdebska et al., 2020).

1.2.Microtubules

The microtubules are the filament type with the stiffest and most complex polymerization and depolymerization dynamics of the three basic filament types in eukaryotic cells. Both actin filaments and microtubules have similar physical properties, however, microtubules are much more rigid due to their larger diameter and tubular structure (Goodson & Jonasson, 2018). The microtubules, polarized cylindrical structures formed by α- and β-tubulin heterodimers, combine to form protofilaments into hollow polymers about 25 nm wide and 1 μm to 100 μm long using GTP energy. (Goodson & Jonasson, 2018;Tang, Mruk & Cheng, 2013). A typical microtubule is commonly formed by the parallel assembly of 13 protofilaments, but there are variations depending on conditions or species. These protofilaments are formed by the interaction of the α-subunit of one dimer with the β-subunit of the other dimer. This organization gives polarity to microtubules. Depending on this polarity, the microtubules are oriented towards two different ends called the + end (α subunit, faster-growing end) or the - end (β subunit, slower-growing end) (Gudimchuk & McIntosh, 2021; Tang et al., 2013). This polarity ensures the directed movement of microtubule-associated motor proteins on the surface of the microtubule. The microtubules are also dynamic, like actin filaments, and their dynamics help organize the cytoskeleton and create forces on other cellular objects (Gudimchuk & McIntosh, 2021). This polarity and dynamism are essential for the function of microtubules in cellular processes such as mitosis, long-distance transport of vesicles and organelles, neuronal differentiation, cell motility, cell migration, and cell polarization (Gudimchuk & McIntosh, 2021; Tang et al., 2013). Flagella, cilia, mitotic spindle, microtubule editing sites, centrosomes, centrioles, spindle pole bodies, basal bodies, and midbody are microtubule-based structures. These structures,

which are especially important for cell division and movement, are formed as a result of the rearrangement of microtubules, motor proteins, and other proteins (Goodson & Jonasson, 2018).

1.3. Intermediate filaments

The intermediate filaments compose an extensive network that connects the cell cortex to intracellular organelles (Etienne-Manneville, 2018). These filaments are networks of 8-12 nm in length, composed of coiling fibrous proteins on top of each other (Melekoglu & Karahan, 2019; Ozdil et al., 2017). The intermediate filaments polymerize spontaneously under appropriate pH and physiological ionic conditions without the need for nucleotides (such as GTP and ATP). The polymerization process has a hierarchical structure that starts with the formation of tetramers (dimers, protofilaments, and protofibrils). On average, eight tetramers interact to make up a unit-length filament containing 32 polypeptides. These unit-length fibers interact in series end-to-end to make up mature intermediate fibers. A typical 10 nm diameter intermediate filament has eight tetramers in its cross-section (Pollard & Goldman, 2018). Unlike microtubules and microfilaments, intermediate filaments are non-polar, more coherent structures. While the destruction of other skeleton elements is done very easily, intermediate filaments are much more permanent (Melekoglu & Karahan, 2019; Ozdil et al., 2017).

The intermediate filaments play a role contribute to many dynamic cellular processes such as resistance to tensile, creation of cell shape, protection of the cell, formation of the nuclear envelope, fixation of some organelles, signal transduction, apoptosis by providing flexibility to the cells (Leube & Schwarz, 2016; Ozdil et al., 2017).

This protein family, consisting of approximately 70 members, is divided into five different groups according to their tissue specificity and similarity in amino acid sequences (Melekoglu & Karahan, 2019; Ozdil et al., 2017). Type I-II-III-IV proteins are located in the cytoplasm and type V proteins are located in the nucleus. Type I and Type II intermediate filaments are basic and acidic keratins that combine into heteropolymeric filaments containing approximately 54 different creatines synthesized in epithelial cells. Type III intermediate filaments consist of homopolymers of desmin (in muscle cells), vimentin (in mesenchymal cells), glial fibrillary acidic protein (astrocytes, glial cells, stellate liver cells), and peripheralin (different neuronal cells). Type IV intermediate filaments are composed of neurofilament-H

(central nervous system), neurofilament-L, M (neurons), and internexin (central nervous system) hetero-homo polymers. Type V intermediate filaments are composed of heteropolymers of Phakinin (in the lens), filensin (in the lens), and nuclear lamins (in all cell types in the nucleus) (Lovery et al., 2015; Melekoglu & Karahan, 2019). Mutations in the genes have been associated with many diseases, from mild skin diseases (swelling) to heart failure (Leube & Schwarz, 2016).

The cytoplasmic intermediate filaments interact with many organelles. These filaments attach the nucleus to the cell cortex with the help of auxiliary proteins (Plectin 1 and Nesprin 3) and take part in the regulation of gene expression (Nishimura, Kasahara, & Inagaki, 2019).

Apart from the three basic cytoskeletal elements, motor proteins also play an important role in the fulfillment of cytoskeletal functions. The motor proteins are important for cell polarity and take part in cell movement. These proteins act unidirectionally on actin filaments or microtubules by changing shape with the energy of ATP-GTP hydrolysis. Myosin, Kinesin, and Dynein are the three main motor protein families. Proteins belonging to the myosin superfamily are functional motor proteins on actin filaments, and many myosin members move toward the hooked end of the actin filament. The microtubule motor proteins include kinesins and dynein. While the kinesins move towards the positive end of the microtubule, the dynein moves towards the negative end of the microtubule (Croos & Dodding, 2019; Ozdil et al., 2017). These motor protein families stimulate and maintain subcellular organization so that cargo proteins and organelles can be transported from one place to another on the actin filaments and the microtubules. However, these proteins have the ability to selectively recognize molecules to be transported (organelle/cargo protein/vesicle) and multiple cargoes (Croos & Dodding, 2019).

2. PROTEINS ASSOCIATED WITH CYTOSKELETAL POLYMERS

2.1. Actin-Associated Proteins

Actin-binding proteins (ABP) are important, integral elements of the actin cytoskeleton. They affect the dynamics of actin filaments by stimulating polymerization or depolymerization of the actin filaments. Many ABPs are involved in the regulation of actin cytoskeleton dynamics. These proteins have many functions such as monomer binding, polymerization, nucleation, depolymerization, branching, cutting, stabilization, scaffolding, filament

separation, and filament crosslinking (Gao & Nakamura, 2022; Pollard, 2016). The functions of ABPs are generally classified according to how they interact with actin and regulate actin dynamics (Gao & Nakamura, 2022). Some motor proteins have more than one function. For example, villin is an ABP with different functions such as crosslinking, nucleation and capping. Apart from ABPs, the actin cytoskeleton can also be regulated by small GTP-binding proteins (such as Cdc42, Rac, Rho, and Ras), and kinases-phosphatases (Izdebska et al., 2020). However, abnormalities in signaling pathways and mutations in the actin and ABPs have been associated with many diseases. This situation has made them potential targets in the diagnosis and treatment of many diseases (Gao & Nakamura, 2022). In Table 1, some of the most well-known actin-binding proteins are classified according to their function.

Table 1: Actin-related proteins and their functions

Nucleation proteins	Arp 2/3, WASP/WAVE Family, FMNL2, Spire
Cross-linking proteins	Scruin, Fascin, Filamin, Fimbrin, Paladin, α-actinin
Cutting and capping proteins	ADF/Kofilin family, Gelsolin family (adseverin, villin, capG, advillin ve supervillin)
Membrane cortex binding proteins	Ezrin, Radixin, Moesin
Proteins that prevent actin polymerization	Profilin
Monomer binding proteins	β-Thymosin, WH2 domain, Twinfilin, Profilin
Stabilizing	Cortactin, Drebrin,

Note: Arp2/3(Actin Related Protein 2/3 complex), FMNL2 (Formin-like protein 2), ADF (Actin polymerizing factor), WASP/WAVE Family (Wiskott-Aldrich syndrome protein/ WASP-family verprolin-homologous protein) (Hohmann & Dehghani, 2019; Pollard, 2016)

2.2. Microtubule-associated proteins

Many microtubule-related proteins have been identified and categorized according to their functions (stabilizers, destabilizers, nucleation proteins, capping proteins, cargo transport proteins, and cross-linkers). As with actin polymers, small GTP binding proteins such as Cdc42, Rac1, and Rho A may also be involved in regulation. In Table 2, some of the most well-known microtubule-binding proteins are classified according to their function (Goodson & Jonasson, 2018).

Table 2: Microtubule-related proteins and their functions

Nucleation proteins	XMAP215, EB, DCX, Tau, CLIP170
Depolymerization proteins	Stathmin
Bundlers and cross-linkers	MAP65/ASE1/PRC1
Microtubule severing proteins	Spastin, katanin
Cargo transport proteins	Kinesin, Dynein
Actin-Microtubule interactions	MACF-1
Stabilizers	CLASP, APC, mDia1, mDia2, Tau, MAP2, MAP4, MAP1b

Note: MAP (Microtubule Associated Protein), CLASP (Cytoplasmic Linker Associated Protein), APC (Adenomatous polyposis coli), DCX (Doublecortin), EB (End binding), CLIP170 (Cytoplasmic linker protein) (Hohman & Dehghani, 2019; Goodson & Jonasson, 2018)

2.3. Intermediate filaments-associated proteins

As with microtubules and microfilaments, intermediate filaments regulate cell homeostasis and cell proliferation through proteins associated with the intermediate filaments. The intermediate filaments perform their functions by interacting not only with structural proteins but also with non-structural proteins. The cytoplasmic intermediate filaments interact with many intracellular organelles (including the nucleus, and centrosome), adhesion sites, integrins, etc., and intermediate filament-related proteins play a role in these interactions. Plectin, Nesprin, plakins, LINC complex (Linker of nucleoskeleton and cytoskeleton), and BPAG1 (Bullous pemphigoid antigen 1) proteins are some of the proteins involved in these functions (Nishimura et al., 2019).

3. REARRANGEMENTS OF ACTIN FILAMENTS

Actin polymerization occurs in three steps including nucleation, elongation, and steady state. The polymerization can be initiated by denovo polymerization (G-Actin) as well as with pre-existing F-actin. As the previously produced F-actin polymerizes, the elongation occurs faster, but if the synthesis occurs denovo, the polymerization begins on a slow lagging

curve rather than linear. The lag phase occurs in the process of which actin nucleation (formation of a dimer and a trimer). After the nucleation, the elongation phase begins and the elongation continues until the actin filament steady state is reached (Gao & Nakamura, 2022). These polymers can be organized into linear bundles or dendritic networks. Linear actin filament formation (G-actin formation) is catalyzed by four major types of nucleator proteins (formin family, Cobl, Lmod, and Spire), while branched-chain F-actin formation is catalyzed only by the Arp2/3 complex. As a result of this catalysis, the actin polymers are attached to the main filaments (existing filaments) at an angle of 70°, and the nucleation and branching process begins. After this stage, the open barbed ends of actin filaments continue to self-extend until terminated by a capping protein (such as gelsolin, or CAPZ). The elongation phase is regulated by anti-capture proteins such as ENA and VASP which are abundant in fast-growing barbed caps, and protect the barbed ends from capping proteins (Wickramarachchi et al., 2010). The intracellular actin concentrations need to be kept at certain levels, and actin-related proteins are used to prevent uncontrolled polymerizations (depolymerization). For example, monomer-binding proteins (such as profile, Tβ4) cleave the actin monomers and prevent the G-actin monomers from polymerizing into F-actin. Likewise, actin polymerization and elongation are inhibited when capping proteins bind to the fast-growing barbed end of the F-actin filament. After polymerization, actin-ATP is hydrolyzed. Hydrolysis of ATP is not required for the polymerization of the actin filaments. On the contrary, bound ATP expedites polymerization and affects affinity. In addition, ATP also affects the structural integrity of the actin filaments. Therefore, ATP is considered an important determinant of actin filament dynamics (DeWane, Salvi & DeMali, 2021). Depolymerization is promoted by the phosphorylation of ATP to ADP followed by the release of γ-phosphate from the F-actin which stimulates the dissociation of ADP-actin (Gao & Nakamura, 2022). Consequently, the actin cytoskeleton reorganizations require the release of the G-actin monomers by depolarization of old F-actin polymers in order to produce new actin filaments (F-actin polymer). The most important role in this regulation process falls to the actin-related proteins, especially the ARP2/3 complex (Wickramarachchi et al., 2010). Regulation of the actin dynamics can also be regulated by small GTPases (such as RhoA, Rac, and Rak Cdc42). The Arp2/3 complex which plays a fundamental role in cytoskeletal regulation is found in an inactive form under normal cellular conditions. These small GTPases, through activation of the WASP and WAVE families, enable the ARP2/3 complex to be activated, and a new nucleation process is begun (Wickramarachchi et al., 2010).

The actin cytoskeleton can also be regulated by post-translational modifications. Many post-translational modifications (such as acetylation, methylation, phosphorylation, and arginylation) of the actin isoforms and the actin-related proteins have been identified. For example, if the β-actin is not arginylated by ATE1, the actin polymerization and interaction with the actin-related proteins are reduced, or if the β- and the γ-actin is not acetylated by NAA80, it causes increased the actin filaments (Parker, Baboolal & Peckham, 2020; Terman & Kashina, 2013). Methylation of the actin at His-73 confers flexibility to the actin and affects its stability. Phosphorylation of Tyr-53 is thought to interfere with polymerization (Terman & Kashina, 2013). Apart from these, phosphorylation of cofilin, an actin-related protein, reduces its interaction with the actin. If phosphorylation is inhibited, actin depolymerization is activated and directs motility (Gao & Nakamura, 2020).
Many cellular activities require reorganization (assembly/disassembly) of the actin cytoskeleton. The actin cytoskeleton rearrangements are best described in cell migration processes, generation of force for cell movement, resistance to external forces, and changes in cell morphology observed during the metastasis stages of cancer cells (DeWane, Salvi & DeMali, 2021). The association of defects in actin cytoskeleton rearrangements and post-translational modifications with many diseases attracts researchers and pushes actin to be a research topic.

4. ACTIN FILAMENTS, ACTIN-RELATED PROTEINS, AND DISEASE

Mutations in the actin and the actin-related proteins which are involved in many functions such as cell division, cell motility, cell growth, adhesion, and migration, cause cellular developmental disorders and dysfunctions of varying degrees. As a result of this process, various diseases occur such as neurodegenerative diseases, inflammatory-autoimmune diseases, muscle diseases, and cancer (Sun et al., 2022). Some of these diseases have been studied in two general classes: diseases caused by mutations in the actin and diseases caused by mutations in actin-related proteins.

There are six different genes encoding α-, β-, and γ- actin isoforms in the human genome. ACTA1, ACTC1, and ACTA2 encode α-actin isoforms (in skeletal, cardiac, and smooth muscle, respectively), ACTB β-actin isoforms, ACTG1, ACTG2 γ-actin isoforms (diffuse expressed, in smooth muscle, respectively). Each of the mutations (most of them are missense mutations) occurring in these genes causes various diseases. Mutations in ACTA1 cause a muscle disease called Nemaline Myopathy (early onset, non-

progressive). Mutations in ACTA2 usually cause familial thoracic aortic aneurysms (due to expression in vascular smooth muscle cells). It is also thought to cause cerebral arteriopathy. More than 70 mutations are seen in ACTC1, the gene encoding the α-actin isoform which is mostly found in heart muscle and these mutations cause heart diseases such as dilated cardiomyopathy, hypertrophic cardiomyopathy, and left ventricular impingement (Parker, Baboolal & Peckham, 2020). Different types of mutations such as missense, early termination, deletion, and frameshift were detected in the ACTB gene, which encodes the β-actin expressed as a housekeeping gene (about 70 mutations) (Cuvertino et al., 2017). Since it is a widely expressed gene, it causes Baraitser-Winter syndrome in which many anomalies are observed (muscle wasting, syndrome-specific face, neuronal migration defects, hearing loss, brain anomalies, etc.). Besides, it has begun to be associated with bleeding disorders. Mutations in the ACTG1 gene often cause deafness or Baraitser-Winter syndrome. Because ACTG2 gene expression is localized in smooth muscle cells in the bladder, intestine, adrenal gland, and prostate, the mutations that occur cause the smooth muscle-related chronic megacystis microcolon-Intestinal hypoperistalsis syndrome (Parker, Baboolal & Peckham, 2020).

In addition, mutations in actin-related proteins also cause many diseases. Diseases associated with mutations in actin-associated proteins are classified as follows from a wide perspective (Table 3).

Table 3: Diseases associated with actin-related proteins

	Disesases	**Mutations**
Neurological diseases		
	Alzheimer	cofilin pathologies
	Parkinson	decreased expression of cofilin
	ALS	mutant or gene expression of insufficient profilin
Muscular dystrophies		
	DMD	dystrophin gene mutations
	SMA	profilin mutations
Infectious diseases		
	AIDS	mutations of the profiling

	Pulmonary Tuberculosis	increased Tβ4 expression
Autoimmune diseases		
	Wiskott-Aldrich syndrome	WASP mutations
	CID	ARPC1B mutation
	Psoriasis	N-WASP, ARPC4 mutations
Cancers		
	Oral squamous cell carcinoma	formin and FHOD1 increased expression
	Leukemia	mDia1
	Lymphomas	FMNL1-PP2
	Pancreatic ductal adenocarcinoma	WDR1
	Colon cancer	mDia2
	Breast cancer	ARP2/ 3, formin
	Stomach cancer	fascin, ARPC3, expression increased
	Lung cancer	profilin, fascin, ezrin, ARP2
Chronic inflammatory diseases		
	myelination and remyelination of the peripheral nervous system	Gelsolin
	Liver damage and inflammation of lung damage	T β 4
	Inflammation of lung damage	Profilin-1
	Inflammatory bowel diseases	SYNPO

Note: ALS (Amyotrophic Lateral Sclerosis), DMD (Duchenne muscular dystrophy), CID (Combined immune deficiency) (Melekoglu & Karahan, 2019; Rottner et al., 2017; Sun et al., 2022; Zhang et al., 2021)

Migrating cells such as metastatic cancers, immune system cells, and fibroblasts use actin cytoskeleton dynamics to generate push-pull forces. Therefore, many studies specifically focus on the relationship between actin

cytoskeleton regulation and cancer (Olson & Machesky, 2021). The Arp 2/3 complex and the WASP/WAVE family are responsible for the formation of membrane protrusions such as lamellipodia, invadopodia, podosome, pseudopodia, and filopodia which are involved in cell invasion, migration and proliferation (Frugtniet et al., 2015). Studies show that the ABPs alters actin dynamics and play a role in the regulation of cancer invasion and metastasis processes. It has been reported that ABP expressions increase or decrease during the migration of cancer cells (Zhang et al., 2021). Moreover, increased expression levels of the ABPs have been associated with poor prognosis in cancer, and the idea that cancer cells can be sensitized to drugs by manipulating the expression of these proteins has emerged (Izdebska et al., 2020). In addition, it is thought that they can be used as potential biomarkers in the diagnosis of cancer due to the increases in expression levels (Zhang et al., 2021).

5. CONCLUSION

The cytoskeleton is a network system that extends from the plasma membrane to the nuclear envelope and even the extracellular matrix, organized by several filaments, motor proteins, and regulatory proteins that connect two neighboring cells. The actin filaments are one of the basic elements of this network system. This filament is involved in many basic processes such as maintaining cell shape, cell movement, cell migration, cell division, endocytosis, and apoptosis. Therefore, it is not surprising that changes in this system lead to pathological consequences. Identifying defects in the cytoskeleton (especially in the actin cytoskeleton) will enable both the pathophysiology of diseases to be determined and the development of new strategies for the diagnosis and treatment of emerging diseases. In addition, understanding the cytoskeletal mechanism in all its aspects will provide answers to many unanswered questions about the cellular system and open new horizons for researchers.

REFERENCES

Bartolák-Suki, E., Imsirovic, J., Nishibori, Y., Krishnan, R., & Suki, B. (2017). Regulation of Mitochondrial Structure and Dynamics by the Cytoskeleton and Mechanical Factors. *Int. J. Mol. Sci.*, *18*(8), 1812. https://doi.org/10.3390/ijms18081812

Blaine, J., & Dylewski, J. (2020). Regulation of the Actin Cytoskeleton in Podocytes. *Cells*, 9 (7), 1700. https://doi.org/10.3390/cells9071700

Crawford, J.M., Bioulac-Sage, P., Hytiroglou, P. (2018).Structure, Function, and Responses to Injury. Macsween's Pathology of the Liver (Seventh Edition), https://doi.org/10.1016/B978-0-7020-6697-9.00001-7

Cross, J.A., & Dodding, M.P. (2019). Motor–cargo adaptors at the organelle–cytoskeleton interface. *Current Opinion in Cell Biology*, 59, 16-23. https://doi.org/10.1016/j.ceb.2019.02.010

Cuvertino S., Stuart H.M., Chandler K.E., Roberts N.A., Armstrong R., Bernardini L., Bhaskar S., Callewaert B., Clayton-Smith J., Davalillo C.H., et al. (2017).ACTB Loss-of-Function Mutations Result in a Pleiotropic Developmental Disorder. *Am. J. Hum. Genet*, 101(6), 1021–1033. https://doi.org/10.1016/j.ajhg.2017.11.006

DeWane, G., Salvi, A.M., & DeMali, D.A. (2021). Fueling the cytoskeleton – links between cell metabolism and actin remodeling. *J Cell Sci*, 134(3), jcs248385. https://doi.org/10.1242/jcs.248385

Etienne-Manneville, S. (2018). Cytoplasmic Intermediate Filaments in Cell Biology. *Annual Review of Cell and Developmental Biology*, 34:1-28 https://doi.org/10.1146/annurev-cellbio-100617-062534

Feher, J. (2017). Cell Structure. Quantitative Human Physiology (Second Edition), 101-119. http://dx.doi.org/0.1016/B978-0-12-800883-6.00010-0

Fletcher, D.A., & Mullins, R.D. (2010). Cell mechanics and the cytoskeleton. *Nature*, 463, 485–492. https://doi.org/10.1038/nature08908

Frugtniet, B., Jiang, W.G., & Martin, T.A. (2015). Role of the WASP and WAVE family proteins in breast cancer invasion and metastasis.*Breast Cancer (Dove Med Press)*, 7, 99–109. https://doi.org/10.2147/BCTT.S59006

Gao, J., & Nakamura, F. (2022). Actin-Associated Proteins and Small Molecules Targeting the Actin Cytoskeleton. *Int J Mol Sci*, 23(4), 2118. https://doi.org/10.3390/ijms23042118

Goodson, H.V., & Jonasson, E.M. (2018). Microtubules and Microtubule-Associated Proteins. *Cold Spring Harb Perspect Biol*, 10, 6: a022608. https://doi.org/10.1101/cshperspect.a022608

Gudimchuk, N.B., & McIntosh, R.J. (2021). Regulation of microtubule dynamics, mechanics and function through the growing tip. *Nature Reviews Molecular Cell Biology*, 22, 777–795. https://doi.org/10.1038/s41580-021-00399-x

Hohmann, T. & Dehghani, F. (2019). The Cytoskeleton A Complex Interacting Meshwork. *Cells*, 8(4), 362. https://doi.org/10.3390/cells8040362

Ilan, Y. (2018). Microtubules: From understanding their dynamics to using them as potential therapeutic targets. *J Cell Physiol*, 234, 7923-7937. https://doi.org/10.1002/jcp.27978

Izdebska, M., Zielińska, W., Hałas-Wiśniewska, M. & Grzanka, A.(2020). Involvement of Actin and Actin-Binding Proteins in Carcinogenesis. *Cells*, 9(10), 2245. https://doi.org/10.3390/cells9102245

Jiang, X., Qin, Y., Kun, L., and Zhou, Y.(2021). The Significant Role of the Microfilament System in Tumors. *Front Oncol*, 11, 620390. https://doi.org/10.3389/fonc.2021.620390

Kim, Y.J., Cho, M.J., Yu, W.D., Kim, M.J., Kim, S.Y., and Lee, J.H. (2022). Links of Cytoskeletal Integrity with Disease and Aging. Cells, 11(18), 2896. https://doi.org/10.3390/cells11182896

Lai, W.F., & Wong, W.T. (2020). Roles of the actin cytoskeleton in aging and age-associated diseases. *Ageing Research Reviews*, 58, 101021. https://doi.org/10.1016/j.arr.2020.101021

Leube, R.E., & Schwarz, N. (2016). Intermediate Filaments. *Encyclopedia of Cell Biology*, 2, 569-578. https://doi.org/10.1016/B978-0-12-394447-4.20056-4

Li, J.Y., & Wu, C.F. (2003). Perspectives on the origin of microfilaments, microtubules, the relevant chaperonin system and cytoskeletal motors— a commentary on the spirochaete origin of flagella. *Cell Research*, 13(4), 219–227. https://doi.org/10.1038/sj.cr.7290167

Lowery, J., Kuczmarski, E.R., Herrmann, H. & Goldman, R.D. (2015). Intermediate Filaments Play a Pivotal Role in Regulating Cell Architecture and Function. *Journal of Biological Chemistry (JBC)*, 290, 28, 17145-17153. https://doi.org/10.1074/jbc.R115.640359

Melekoğlu, A., & Karahan, O.(2019). Structures of Cytoskeleton and Disease Interactions [Hücre İskeleti Yapıları ve Hastalıklarla Etkileşimleri].

Acta Medica Alanya, 3, 2, 197-202. https://doi.org/10.30565/medalanya.528070

Merino, F., Pospich, S., & Raunser, S. (2020). Towards a structural understanding of the remodeling of the actin cytoskeleton. *Semin Cell Dev Biol*, 102, 51–64. https://doi.org/10.1016/j.semcdb.2019.11.018

Nishimura, Y., Kasahara, K., & Inagaki, M. (2019). Intermediate filaments and IF-associated proteins: from cell architecture to cell proliferation. *Proc Jpn Acad Ser B Phys Biol Sci*, 95, 8:479-493. https://doi.org/10.2183/pjab.95.034.

Olson, M.F., & Machesky, L.M. (2021). MICAL2 fine-tunes Arp2/3 for actin branching. *J Cell Biol.*, 220, 8, e202106176. https://doi.org/10.1083/jcb.202106176

Omary, M.B., Coulombe, P.A., & McLean, W.H.I. (2004). Intermediate Filament Proteins and Their Associated Diseases. *N Engl J Med*, 351:2087-2100. https://doi.org/10.1056/NEJMra040319

Ozdil, B., Gürel, C., Kılıç, K.D., Kuşçu, G.C., Adalı, Y. & Aktug, H. (2017). Hücre içi trafik ve hücre davranış özellikleri [Intracellular trafficking and cell behaviour characteristics]. *Ege Journal of Medicine*, 56(1), 102-110.

Parker, F., Baboolal, T.G. & Peckham, M. (2020). Actin Mutations and Their Role in Disease. *Int J Mol Sci*, 21(9), 3371. https://doi.org/10.3390/ijms21093371

Pollard, T.D. (2016). Actin and Actin-Binding Proteins. *Cold Spring Harb Perspect Biol*, 8 (8), a018226. https://doi.org/10.1101/cshperspect.a018226.

Pollard, T.D., & Goldman, R.D. (2018). Overview of the Cytoskeleton from an Evolutionary Perspective. Cold Spring Harb Perspect Biol, 10,7, a030288. https://doi.org/10.1101/cshperspect.a030288

Sun, J., Zhong, X., Fu, X., Miller, H., Lee, P., Yu, B., Liu, C. (2022). The Actin Regulators Involved in the Function and Related Diseases of Lymphocytes. *Front Immunol*, 16(13), 799309. https://doi.org/10.3389/fimmu.2022.799309.

Svitkina, T. (2018). The Actin Cytoskeleton and Actin-Based Motility. *Cold Spring Harb Perspect Biol*, 10(1), a018267. https://doi.org/10.1101/cshperspect.a018267

Tang, E.I., Mruk, D.D., & Cheng, C.Y. (2013). MAP/microtubule affinity-regulating kinases, microtubule dynamics, and spermatogenesis.

Journal of Endocrinology, 217(2), 13–23. https://doi.org/10.1530/JOE-12-0586

Terman, J.R., & Kashina, A. (2013). Post-translational Modification and Regulation of Actin. *Curr Opin Cell Biol*, 25(1): 30–38. https://doi.org/10.1016/j.ceb.2012.10.009

Wickramarachchi, D., Theofilopoulos, A.N., & Kono, D.H. (2010). Immune Pathology Associated with Altered Actin Cytoskeleton Regulation, *Autoimmunity*, 43(1), 64–75. https://doi.org/10.3109/08916930903374634

Wickstead, B., & Gull, K. (2011). The evolution of the cytoskeleton. *J Cell Biol*, 194(4), 513–525. https://doi.org/10.1083/jcb.201102065

Zhang, Y-G. Niu, J-T., Wu, H-W., Si, X-L., Zhang, S-J., Li, D-H., Bian,T-T., Li, Y-F., & Yan, X-K. (2021). Actin-Binding Proteins as Potential Biomarkers for Chronic Inflammation-Induced Cancer Diagnosis and Therapy. *Anal Cell Pathol (Amst*), 6692811. https://doi.org/10.1155/2021/6692811

CHAPTER 4

MINDFULNESS IN CHILD AND ADOLESCENT MENTAL HEALTH

Dr. Neslişah GÜR KURÇALOĞLU[1]

[1]Samsun Training and Research Hospital, Child and Adolescent Psychiatry Clinic, Samsun, Turkey. neslsahgur@gmail.com,Orcid ID: 000-0002-8070-0001X

INTRODUCTION

The concept of mindfulness is based on eastern meditation and Pali language. Mindfulness is characterized by focusing on the present moment with an attitude of curiosity, openness, and acceptance (Siegel et al., 2009). In this section, the concept of mindfulness, mindfulness-based therapies, and their place in child and adolescent mental health will be discussed.

Mindfulness focuses on mental processes that do not necessarily reflect something relevant to one's self and realities, rather than reconstructing disturbing thoughts. It provides acceptance of unpleasant experiences and experiential learning (Sharma, 2014).

Shapiro et al. (2006) suggested that mindfulness includes three mechanisms. These mechanisms are intention, attention, and attitude. They stated that these three mechanisms are parts of a single cyclical process.

Mindfulness meditation helps people to give creative reactions to the situation they are in and to get rid of undesired automatic reactions (Nila et al., 2016).

Mindfulness-based interventions are suggested to have positive effects in the treatment of both psychological and physical symptoms (Shapiro, 2006).

Mindfulness is a non-judgmental awareness of experience. It involves intentional participation in one's mental processes. Mindfulness enables us to look at things more flexibly and maintain attention. Teaching mindfulness-based skills to children increases such skills as maintaining children's attention and managing emotions. Additionally, teaching mindfulness techniques to parents improves family relationships (Harnett & Dawe, 2012).

Attention deficit and hyperactivity disorder (ADHD) is a common neurobehavioral disorder characterized by inattention, hyperactivity, and impulsivity and related functional impairment. Although ADHD first manifests its symptoms in childhood, it often continues in adult life. Treatment includes drug and behavioral therapy interventions. A considerable number of studies have showed the efficacy of pharmacological therapy for reducing ADHD symptoms in patients with ADHD (Pliszka, 2007). However, additional approaches are frequently used. Mindfulness meditation can be recommended to increase attention and reduce stress. In a study conducted with adults and adolescents with ADHD, the applicability of mindfulness education was tested. As a result of the research, most of the participants reported their satisfaction. It was reported that there was a decrease in anxiety and depressive symptoms (Zylowska, 2007).

A positive correlation was determined between mindfulness and life satisfaction in a study conducted with adolescents in China (Jianfeng et al., 2016). Mindfulness-based trainings have significant benefits. Many studies have included clinical examples in their studies to research the effectiveness of mindfulness. In a study conducted with university students, it was determined that group-based mindfulness study increased life satisfaction. Additionally, it

was observed that psychological distress decreased in students. As a result of the study, it was stated that a short mindfulness intervention could be useful in increasing life satisfaction for those without serious psychological problems (Harnett et al., 2010).

Regarding secondary school students, a study was conducted to measure the effectiveness of The Mindfulness in School Program (MISP). 522 students aged between 12-16 were included in the study. After the program, less depressive symptoms and less stress in the students were reported (Kuyken et al., 2013).

Mindfulness-based therapies are increasingly preferred. Mindfulness involves bringing one's attention to the present moment intentionally and can be applied together with meditation exercises (Baer, 2003).

After cognitive-behavioral therapies, mindfulness-based therapies have come to the fore as third-wave methods. We can group mindfulness-based therapies under four headings. These are:

- Mindfulness-based stress reduction program, which is a group therapy developed by Kabat-Zinn (1982),
- Mindfulness-based cognitive therapy developed to prevent relapse in depression in people who have previously had depression (Segal, Williams & Teasdale, 2002),
- Acceptance and commitment therapy, which emphasizes acceptance and uses activities whose awareness is based on daily life adaptation (Hayes, 2004),
- Dialectical behavior therapy used in the treatment of borderline personality disorders and emotion regulation (Linehan, 1993).

Mindfulness-Based Stress Reduction (MBSR)

Stress is one of the public health problems of our age. The most frequently applied training that reduces mindfulness-based stress levels is mindfulness-based stress reduction (MBSR). Jon Kabat-Zinn has developed MBSR training inspired by Zen meditation and yoga. MBSR increases people's awareness and focus on the present (Kabat-Zinn, 1982). MBSR is a structured group program that uses mindfulness techniques to reduce pain in psychiatric disorders and psychosomatic complaints. MBSR has been reported to reduce stress levels in healthy individuals as well as being an effective meditation in many mental and physical disorders (Chiesa and Serretti, 2009).

MBSR includes eight-week group classes. The lessons are often held in two and a half to three-hour sessions in the first weeks. After the sixth week, silent mindfulness techniques are taught in a full day. The number of people in the group can be up to thirty. This program aims to develop awareness of the instantaneous experience of mental processes. Within the scope of MBSR, physical awareness is emphasized. A wide range of mindfulness exercises such as body scan exercises are taught to increase awareness. Body scan exercise is

performed in forty-five-minute sessions in which the client's attention is on the body and scans the body parts alternately while lying eyes closed. The client focuses on the sensations from the body while scanning the body parts. Another mindfulness exercise used in MBSR training is sitting meditation. The person closes his/her eyes and sits comfortably and calmly in sitting meditation. Then, the person is asked to focus his/her attention on breathing sensations. Additionally, in MBSR training, Hatha yoga poses can be used to increase awareness of body sensations. These exercises are used in daily life activities. The clients are asked to practice mindfulness exercises in daily activities along with the group studies. Participants are asked to perform mindfulness exercises six days a week. Duration of daily mindfulness exercises should be at least forty-five minutes. Clients can use audio recordings to do the exercises in their daily routines. It is important to focus on the present moment while doing exercises. Thoughts and factors that distract attention from the present moment are noted. In this way, emotional and thought awareness is formed in the clients. Negative and critical thoughts are also allowed to be felt without being judged. Clients realize that their emotions and thoughts are constantly fluctuating through mindfulness exercises (Baer, 2003). Thus, the person experiences that emotions and thoughts are temporary in nature.

MBSR reduces the emotional response in the person and increases cognitive evaluation. Thus, it is aimed to change the relation of the person with stressful events and thoughts (Teasdale, Segal, and Williams, 1995).

It has been reported that MBSR reduces ruminative thoughts, anxiety, and stress and increases empathy and self-compassion in individuals (Chiesa & Serretti, 2009).

MBRS has been reported to increase distress tolerance and resilience (Nila, 2016).

In a systematic review, it was reported that MBSR was also effective in reducing stress in healthy individuals. The same review proposed the MBSR program to be included as a stress reduction approach in teaching stress management (Sharma & Rush, 2014).

Information on the efficacy of MBRS in children and adolescents is limited. In a study researching the effectiveness of MBRS on mental symptoms in young people, volunteer adolescents aged between 12-18 years were included. Eight-week MBRS was applied to the volunteers in the study. As a result of the study, MBRS was reported to be effective in internalization problems such as depression, anxiety, and somatization in adolescents. In addition, MBRS was reported to have a positive effect on coping skills (Vohra et al., 2019).

The effectiveness of school-based mindfulness education was investigated to reduce the negative effects of stress and trauma on secondary school students. The training in the study was adapted from the MBRS program. Results of the research support that mindfulness education can reduce

trauma symptoms and improve the negative effects of stress in secondary school students (Sibinga et al., 2016).

In a study conducted with 27 adolescents aged between 12-17 years with chronic diseases, the applicability of the mindfulness-based meditation program for adolescents experiencing chronic pain and anxiety symptoms was demonstrated. It was reported that mindfulness-based methods could provide an integrative treatment by sensing the body and mind at the same time (Suc et al., 2022).

Effectiveness of the MBSR program was evaluated in a study conducted with 102 adolescents who received psychiatric treatment. When compared to the traditionally treated control group, it was determined that adolescents included in the MBSR program had reduced symptoms of depression, anxiety, and somatization. It was reported that the self-esteem and sleep quality of the adolescents included in the MBRS program increased. Additionally, a significant increase was noted in the functionality scores of these adolescents. Consequently, it was suggested that MBSR may help the psychiatric treatment of outpatient adolescents (Biegel et al., 2009).

MBSR was reported to reduce disease-related stress in adolescents with cardiac diagnosis who experienced psychosocial distress. In addition, after treatment, it was determined that coping skills increased and anxiety and depression scores decreased in adolescents (Freedenberg et al., 2017).

Mindfulness-Based Cognitive Therapy (MBCT)

Mindfulness-based cognitive therapy (MBCT) has been developed to prevent recurrence in the treatment of mood disorders. This therapy approach integrates mindfulness meditation with cognitive therapy techniques. Body scan meditation, sitting meditation, walking meditations, and breathing exercises are used. Cognitive behavioral therapy deals with one's negative thoughts about oneself, other people, and the world. On the other hand, MBCT allows the person to experience these thoughts by accepting them gently, instead of changing the thoughts.

Depression affects one in five people during lifetime. It may progress as recurrent depressive episodes (Rycroft-Malone, 2007). MBCT helps to prevent recurrence and learn skills to stay well in people with major depression. It has been developed as a group-based psychosocial approach (Segal, 2002).

Depressogenic thinking activated by dysphoria may cause recurrence of the disease in depressed patients. MBCT is a group intervention based on cognitive therapy and mindfulness that allows the depressive patient to separate from depressogenic thinking. MBCT significantly reduces recurrence in major depression (Teasdale et al., 2000).

Dialectical Behavior Therapy (DBT)

Dialectical behavior therapy (DBT) has been developed for people who engage in high-risk behaviors, and it includes acceptance, change and dialectic. It was first developed for chronic, suicidal Borderline Personality Disorder cases. DBT consists of individual therapy, phone coaching, and a therapist consultation team. The individual therapy is sixty-minute sessions once a week. While accepting the individual, alternative methods are created for risky and problematic behaviors. In DBT skill training group, the number of clients is maximum 10. Basic skills are learned in 6 months in standart DBT skill training. Emotion regulation skills are mindfulness skills, interpersonal effectiveness skills, stress tolerance skills and emotion regulation skills (Neacsiu et al., 2014).

Mindfulness module aims to teach the skills of recognizing and allowing feelings in the present moment without judging and hindrance. Mindfulness skills are central to DBT, and they are the first skills taught. Mindfulness skills support other DBT skills (Fassbinder et al., 2016).

In a study by Verheul et al., 58 female patients with borderline personality disorders were included. As a result of the study, it was observed that dialectical behavior therapy significantly reduced self-harm and impulsive behaviors in female patients with borderline personality disorders compared to the control group. In the same study, it was reported that patients who received DBT had lower treatment discontinuation rates within one year compared to the control group (Verheul et al., 2003).

The theoretical frameworks of DBT can be particularly useful for adolescents with emotional dysregulation (Groves et al., 2012).

In a case series study conducted by Baudinet et al. (2021) with adolescents, it was reported that dialectical behavior therapy adapted for adolescents can be effective in the treatment of depression and eating disorders. Treatment was reported to show further evaluation, especially for underweight adolescents with eating disorders.

Acceptance and Commitment Therapy (ACT)

Behavioral therapies are divided into three generations: traditional behavior therapy, cognitive behavioral therapy, and third-generation therapy. Acceptance and commitment therapy (ACT) is a widely used approach in the context of third-wave cognitive behavioral therapies. ACT acts through different processes from traditional cognitive behavioral therapy. Rather than dealing with symptoms or syndromes individually, ACT focuses on the process. ACT has a hexagonal model consisting of six basic processes (Hayes, 2004). Main components of hexagon model for psychological inflexibility are attentional inflexibility, confusion of values, inertia or impulsivity, conceptual self, cognitive fusion, and avoidance. And the components of psychological

flexibility are flexible attention, contact with values, self-as-context, cognitive diffusion, and acceptance (Hayes, Pistorello & Levin, 2012).

ACT deals with psychological inflexibility and aims for psychological flexibility. Psychological flexibility and 6 psychological change processes are crucial in ACT. These processes are acceptance, diffusion, being present, self-as-context, values, and committed action (Twohig, 2012). Acceptance is embracing undesirable experiences with mindfulness rather than avoiding them.

According to ACT, the combination of these components demonstrates psychological flexibility, while the absence of them predicts psychological inflexibility. Psychological inflexibility is associated with mental problems and impairment in functionality. The increase in mental problems as a result of psychological inflexibility causes cognitive fusion and experiential avoidance. Cognitive fusion prevents the person from effectively coming into contact with the consequences of his/her actions and producing functional solutions to problems. In vital avoidance, the person avoids disturbing thoughts and feelings. Vital avoidance narrows one's behavioral repertoire and prevents seeing the possible positive consequences of behaviors (Twohig, 2012).

In a randomized controlled trial conducted with thirty adolescents diagnosed with depression, ACT interventions were compared with cognitive-behavioral therapy interventions. It was reported that the severity of depression symptoms of adolescents who underwent ACT decreased significantly compared to the control group. Additionally, it was stated that the depression symptom severity continued to improve in the ACT group after treatment (Hayes, Boyd & Sewell, 2011). In two pilot studies, one conducted in Australia and the other in Sweden, the effects of school-based ACT applications on depression and stress symptoms were investigated. Short-term (eight sessions) ACT application was reported to have significant reducing effect on depressive symptoms, perceived stress level, and psychological inflexibility. In addition, it was observed that mindfulness skills of adolescents increased after ACT application. It was indicated that ACT interventions could be applied to reduce depressive symptoms and stress for adolescents at school. (Livheim et al., 2014).

The effects of a 5-week computer-based intervention program based on ACT principles on the mental health of adolescents were investigated. 243 adolescents aged between 15-16 years were included in the study. It was reported that computer-based ACT intervention could be an effective intervention in preventing mental disorders and improving well-being in adolescents (Lappalainen, 2021).

CONCLUSION

There are many studies on the positive effects of mindfulness-based therapeutic techniques. There is significant evidence of the effectiveness of

mindfulness-based approaches for adults with chronic illness or mental problems. On the other hand, there is limited evidence on the use of mindfulness-based interventions in child and adolescent population. Childhood and adolescence are developmental periods that shape mental health in adult life. Interest in treatment practices for the social and psychological well-being of children and young people is increasing. In a study by Burke, (2009) when investigating mindfulness-based approaches in children and adolescents, he emphasized the importance of studies with a strong methodology that included standardized interventions rather than feasibility studies. Further research is needed to understand the social, psychological, and behavioral effects of mindfulness-based therapies on children and adolescents and to explore their mechanisms. In addition, the addition of mindfulness skills to educational programs in schools can provide a holistic educational approach which protects the mental health of children and adolescents.

REFERENCES

Baer, R. (2003). Mindfulness as a clinical intervention. *Clinical Psychology Science and Practice*, 10(2), 125-143. https://doi.org/10.1093/clipsy.bpg015

Baudinet, J., Stewart, C., Bennett, E., Konstantellou, A., Parham, R. et al. (2021). Radically open dialectical behaviour therapy adapted for adolescents: A case series. *BMC Psychiatry*, 21, 462. https://doi.org/10.1186/s12888-021-03460-3

Biegel, GM. Et al. (2009). Mindfulness-based stress reduction for the treatment of adolescent psychiatric outpatients: A randomized clinical trial. *J Consult Clin Psychol.* 77(5), 855-866. https://doi.org/10.1037/a0016241

Burke, CA. (2010). Mindfulness-based approaches with children and adolescents: A preliminary review of current research in an emergent field. *J Child Fam Stud.* 19, 133-144. https://doi.org/10.1007/s10826-009-9282-x

Chiesa, A. & Serretti, A. (2009). Mindfulness-based stress reduction for stress management in healthy people: A review and meta-analysis. *The Journal of Alternative and Complementary Medicine,* 15(5), 593-600. https://doi.org/10.1089/acm.2008.0495

Fassbinder, E., Schweiger, U., Martius, D., Brand-de Wilde, O. & Arntz, A. (2016). Emotion regulation in schema therapy and dialectical behavior therapy. *Frontiers in Psychology*, 7, 1373. https://doi.org/10.3389/fpsyg.2016.01373

Freedenberg, VA., Hinds, PM., Friedmann, E. (2017). Mindfulness-based stress reduction and group support decrease stress in adolescents with cardiac diagnoses: A randomized two-group study. *Pediatr Cardiol.* 38, 1415-1425. https://doi.org/10.1007/s00246-017-1679-5

Harnett, PH. & Dawe, S. (2012). Review: The contribution of mindfulness-based therapies for children and families and proposed conceptual integration. *Child Adolesc Ment Health.* 17(4), 195-208. https://doi.org/10.1111/j.1475-3588.2011.00643.x

Harnett, PH., Whittingham, K., Puhakka, E., Hodges, J., Spry, C. & Dob, R. (2010). The short-term impact of a brief group-based mindfulness therapy program on depression and life satisfaction. *Mindfulness.* 1, 183-188. https://doi.org/10.1007/s12671-01

Hayes, SC. (2004). Acceptance and commitment therapy, relational frame theory and the third wave of behavior therapy. *Behavior Therapy,* 35, 639-665. https://doi.org/10.1016/S0005-7894(04)80013-3

Hayes, SC., Luoma, JB., Bond, FW., Masuda, A., Lillis, J. (2006). Acceptance and commitment therapy: Model, processes and outcomes. *Behaviour Research and Therapy,* 44, 1-25. https://doi.org/10.1016/j.brat.2005.06.006

Hayes, L., Boyd, CP., Sewell, J. (2011). Acceptance and commitment therapy for the treatment of adolescent depression: A pilot study in a psychiatric outpatient setting. *Mindfulness*, 2, 86-94. https://doi.org/10.1007/s12671-011-0046-5

Groves, S., Backes, HS., van den Bosch, W., Miller, Alec. (2012). Dialectical behaviour therapy with adolescents: A review. *Child and Adolescent Menatl Health*. 17(2), 65-75. https://doi.org/10.1111/j.1475-3588.2011.00611.x

Jianfeng, T., Wu, Y., Hongwei, M. & Yulan, Y. (2016). Adolescents' core self-evaluations as mediators of the effect of mindfulness on life satisfaction. *Social Behavior and Personality: An International Journal,* 44(7), 1115-1122. https://doi.org/10.2224/sbp.2016.44.7.1115

Kabat-Zinn, J. (1982). An outpatient in behavioral medicine for chronic pain patients based on the practice of mindfulness meditation: Theoretical considerations and preliminary results. *General Hospital Psychiatry*, 4, 33-47. https://doi.org/10.1016/0163-8343(82)90026-3

Kuyken, W., Weare, K., Ukoumunne, OC., Vicary, R., Motton, N. et al. (2013. Effectiveness of the mindfulness in schools programme: Non-randomised controlled feasibility study. *The British Journal of Psychiatry*, 203(2), 126-131. https://doi.org/10.1192/bjp.bp.113.126649

Lappalainen, R., Lappalainen, A., Puolakanaho, R., *Hirvonen*, K., Eklund, T. Et al. (2021). The youth compass- the effectiveness of an online acceptance and commitment therapy program to promote adolescent mental health: A randomized controlled trial. *Journal of Contextual Behavioral Science*, 20, 1-20. https://doi.org/10.1016/j.jcbs.2021.01.007

Linehan, MM. (1993). Cognitive-behavioral treatment of borderline personality disorder. *New York, NY: Guilford Press.* 3-56

Livheim, F., Hayes, L., Ghaderi, A., Magnusdottir, T., Hogfeldt, A. et al. (2014). The effectiveness of acceptance and commitment therapy for adolescent mental health: Swedish and Australian pilot outcomes. *Journal of Child and Family Studies*, 24, 1016-1030.https://doi.org/10.1007/s10826-014-9912-9

Neacsiu, AD., Eberle, JW., Kramer, R., Wiesmann, T. & Linehan, MM. (2014). Dialectical behavior therapy skills for transdiagnostic emotion dysregulation: A pilot randomized controlled trial. *Behaviour Research and Therapy*, 59, 40-51. https://doi.org/10.1016/j.brat.2014.05.005

Nila, K., Holt, DV., Ditzen, B., Aguilar-Raab, C. (2016). Mindfulness-based stress reduction (MBSR) enhances distress tolerance and resilience throug changes in mindfulness. *Ment Health Prev*, 4(1), 36-41. https://doi.org/10.1016/j.mhp.2016.01.001

Pliszka, S. (2007). Practice parameters for the assessment and treatment of children and adolescents with attention-deficit hyperactivity disorder. *J*

Am Acad Child Adolesc Psychiatry, 46 (7), 894- 921. https://doi.org/10.1097/chi.0b013e318054e724

Rycroft-Malone, J., Gradinger, F., Griffiths, HO., Crane, R., Gibson, A. et al. (2007). Accessibility and implementation in the UK NHS services of an effective depression relapse prevention programme: learning from mindfulness-based cognitive therapy through a mixed-methods study. *Health Services and Delivery Research.* 5(14). https://doi.org/10.3310/hsdr05140

Segal, ZV., Teasdale, J., Williams, M., Gemar, MC. (2002). The mindfulness-based cognitive therapy adherence scale: inter-rater reliability, adherence to protocol and treatment distinctiveness. *Clinical Psychology & Psychotherapy.* 9(2), 131-138. https://doi.org/10.1002/cpp.320

Sibinga, EM., Webb, L., Ghazarian, SR. & Ellen, JM. (2016). School-based mindfulness instruction: An RCT. *Pediatrics,* 137(1), e20152532. https://doi.org/10.1542/peds.2015-2532

Siegel, RD., Germer, CK. & Olendzkı, A. (2009). 'Mindfulness: what is it? Where did it come from?', F. Didonna (Ed), *In Clinical Handbook of Mindfulness,* (17-35), New York, Springer

Shapiro, SL., Carlson, LE., Astin, JA. & Freedman, B. (2006). Mechanisms of mindfulness. *Journal of Clinical Psychology,* 62(3), 373- 386. https://doi.org/10.1002/jclp.20237

Sharma, E. (2014). Mindfulness based interventions for children. *J Indian Assoc Child Adolesc Ment Health.* 10(1), 1-8. https://doi.org/10.1177/09731342201401

Sharma, M. & Rush, SE. (2014). Mindfulness-based stress reduction as a stress management intervention for healthy individuals: A systemic review. *Journal of Evidenced-Based Complementary and Alternative Medicine,* 19(4), 271-286. https://doi.org/10.1177/2156587214543143

Suc, A., Cayzac, D., Iannuzzi, S., Garnier, C., Bonneau, B., Sommet, A. (2022). Peacefull: A French mindfulness-based intervention for adolescents with chronic pain a feasibility study. *Archives de Pédiatrie.* https://doi.org/10.1016/j.arcped.2022.06.006

Teasdale, JD., Segal, ZV., Williams, JMG. (1995). How does cognitive therapy prevent depressive relapse and why should attentional control (mindfulness) training help? *Behav Res Ther,* 33, 25-39. https://doi.org/10.1016/0005-7967(94)E0011-7

Teasdale, JD., Segal, ZV., Williams, JMG., Ridgeway, VA., Soulsby, JM. & Lau, MA. (2000). Prevention of relapse/ recurrence in majör depressions by mindfulness-based cognitive therapy. *Journal of Consulting and Clinical Psychology,* 68, 615-623. https://doi.org/10.1037/0022-006X.68.4.615

Twohig, M. (2012). Introduction: The basics of acceptance and Commitment therapy. *Cognitive and Behavioral Practice*, 19, 499-507. https://doi.org/10. 1016/j.cbpra.2012.04.003

Verheul, R., Van Den Bosch, LM., Koeter, MW., De Ridder, MA., Stijnen, T. et al. (2003). Dialectical Behavior Therapy for Women with Borderline Personality Disorder. *Br J Psychiatry*, 182, 135-40. https://doi.org/10.1192/bjp.182.2.135

Vohra, S., Punka, S., Sibinga, E., Baydala, L., Wikman, E., Singhal, A. et al. (2019). Mindfulness-based stress reduction for mental health in youth: A cluster randomized controlled trial. *Child Adolesc Ment Health*, 24(1), 29-35. https://doi.org/10.1111/camh.12302

Zylowska, L., Ackerman, DL., Yang, MH., Futrell, JL., Horton, NL., Hale, ST. et al. (2007). Mindfulness meditation training with adults and adolescents with ADHD. *Journal of Attention Disorders*, 11, 737–746. https://doi.org/10.1177/108705470730850

CHAPTER 5

ANATOMY, ASSESSMENT AND MOBILIZATION OF THE KNEE JOINT

Asst. Prof. Dr. Halil YILMAZ[1]

[1]Ordu University, Medicine Faculty, Department of Anatomy, Ordu, TÜRKİYE. halilyilmaz@gmail.com, Orcid ID: 0000-0002-8234-4901

The knee joint is the largest and most complex joint in the body (Vaienti, Scita, Ceccarelli, & Pogliacomi, 1885). There are two joints in the knee, the tibiofemoral joint and the patellofemoral joint (Loudon, 2016). In fact, the opposing joint surfaces that make up the knee joint are not compatible with each other and create a potential for dislocation, but dislocations are rarely seen clinically due to the strong ligaments. Knee traumas are very common in clinics. Apart from reasons related to external factors such as the knee being in the most unprotected place in accidents or being the part that touches the ground first in falls, the presence of meniscus and internal ligaments to hold the joint together in the joint and often the deterioration of the relationship between them cause knee pathologies (John et al., 2016). The main joint type is the synovial joint. Due to the unique joint structure of the knee joint, some researchers classify it as a bicondylar joint, while some sources classify it as a ginglymus joint. Since the femur has two condyles according to the convex articular surface, it is classified as a bicondylar joint, while bicondylar joints should have a double joint capsule, while the knee joint has a single joint capsule (Fox, Bedi, & Rodeo, 2012). While the ginglymus joint type only allows flexion and extension movements in the transverse plane, the knee joint can perform some rotation after 30 degrees of flexion. For this reason, many sources state that it is more appropriate to call it a bicondylar joint (Russell, Zhu, Hey, Vaidyanathan, & Ellison, 2018).

The proximal part of the joint is mainly composed of the condyles of the femur. When viewed distally between the condyles of the femur, the pit (intercondylar fossa) is seen, and when viewed from the distal, the articular surface (patellar surface) articulating with the patella is seen (Fox et al., 2012)

The articular surface of the tibial condyles forms the distal part of the joint. The articular surface on the lateral side is smaller and rounder, while the articular surface on the medial side is wider and oval (Kambic 2017). The difference between the articular surfaces of the tibial condyles affected the shapes of the meniscus sitting on the articular surfaces and constitutes the main reason for the difference in the clinical manifestations of the inner and outer meniscus (Russell et al., 2018).

Since it is larger than the articular surface in the femoral condyles and the articular surface in the tibial condyles, the femur slides over the tibia as the leg flexes. As the flexed leg goes into extension, the tibia comes forward as the femur goes backwards (Freeman & Pinskerova, 2003).

In addition, the articular surface, which forms the posterior part of the patella, which is the largest sesamoid bone of the body, also joins the joint (Steinmetz et al., 2020).

Apart from the joint capsule, which protects the integrity of the knee joint, there are both intra-capsular and extra-capsular ligaments (Vaienti et al., 1885).

Joint capsule: The fibrous membrane of the capsule has a strong and complex structure with the inclusion of extensions of the external ligaments. The synovial membrane of the knee joint is the most complex and largest synovial sac in the body. This sac forms the suprapatellar bursa in the upper part of the patella, and this bursa facilitates the movement of the quadriceps femoris muscle tendon. There is an infrapatellar fat pad between the synovial membrane and the patellar ligament (Hoffa's fat pad) (Eymard & Chevalier, 2016).

Extra-capsular Ligaments of Knee Joint

Patellar ligament: The main structure of this ligament, which is about 8 cm long and 2 cm wide, is formed by the tendon of the middle part of the quadriceps femoris muscle. The patellar ligament has two sisters on its sides. Extensions of the fibers of the vastus medialis muscle form the medial patellar retinaculum, and extensions of the vastus lateralis muscle form the lateral patellar ligament (Bennett et al., 2021).

Oblique popliteal ligament: It starts from the medial condyle of the tibia and attaches to the lateral condyle of the femur. Passage of the popliteal artery from the posterior aspect of this ligament has clinical and surgical significance (Fam et al., 2013).

Arcuate popliteal ligament: It is a Y-shaped ligament, one arm of the letter Y is attached to the head of the fibula and the other arm is attached to the posterior intercondylar area, while its base is attached to the posterior epicondyle of the femur (Song et al., 2018).

Tibial collateral ligament: It is also known clinically as the medial collateral ligament of knee. It is a broad and flat ligament that extends from the medial epicondyle of the femur to the medial condyle of the tibia. It is attached to the medial meniscus by the fibrous capsule. Injuries to these 3 structures affect each other due to the attachment of the medial meniscus in the anterior cruciate ligament. These three structures are called the unhappy triad. Medial collateral ligament injury is more common than the lateral collateral ligament. Usually, this ligament is injured by lateral force on the knee (Andrews, Lu, Mckean, & Ebraheim, 2017).

Fibular collateral ligament: Known in clinical medicine as the lateral collateral ligament of the knee, and it extends to the head of the fibula on the lateral condyle of the femur. While the proximal part of the ligament is covered by the tendon of biceps femoris muscle, the fibers of this tendon are mixed with the ligament distally. Unlike the medial collateral ligament, this ligament is not associated with the lateral meniscus and joint capsule. Lateral inferior genicular artery passes between the joint capsule and this ligament. In surgical operations

or physical therapy, it is necessary to pay attention to its close neighborhood to this artery (Kane et al., 2018).

Intra-capsular Ligaments of Knee Joint

Anterior Cruciate Ligament (ACL): It is the anterior of a pair of cruciate ligaments in the knee joint. Its origin is the lateral condyle of the femur and ends in the tibia anterior intercondylar area. Its distal part is attached to the medial meniscus. The function of this ligament is to prevent the tibia from sliding forward during leg flexion (Filbay & Grindem, 2019).

Posterior Cruciate Ligament (PCL): It is the posterior one of the cruciate ligaments and is shorter, straighter and thicker than the ACL. It begins above the lateral condyle of the femur and ends below at the posterior intercondylar area. The distal part of the PCL fuses with the lateral meniscus. When leg flexion is performed in the knee joint, it prevents the tibia from moving forward and the femur backwards forward (Pache et al., 2018).

Meniscuses

In the knee joint, the articular surfaces of the femoral and tibial condyles are not compatible with each other. It is a double formation of fibrous cartilage to compensate for this mismatch. The one on the side of the tooth is called the lateral meniscus, and the one on the inside is called the medial meniscus (Beaufils & Pujol, 2017).

Lateral meniscus: Compared to the medial meniscus, the ends are more closed and have the shape of the letter C. Its anterior end attaches to the anterior intercondylar area, and its posterior end to the posterior intercondylar area. The distal portion of the PCL fuses with the lateral meniscus. In this section, two ligaments run anterior and posterior to the PCL. The anterior one is called the anterior meniscofemoral ligament, and the posterior one is called the posterior meniscofemoral ligament (Kawashima & Tagaki, 2021).

Medial meniscus: In this section, two ligaments run anterior and posterior to the PCL. The anterior one is called the anterior meniscofemoral ligament, and the posterior one is called the posterior meniscofemoral ligament. The ACL attaches anteriorly to the medial meniscus. The peripheral part of the medial meniscus is fused with the medial collateral ligament and is affected by trauma to this ligament. Medial meniscus injuries are 2 times more common than lateral meniscus. The lateral and medial meniscus are connected anteriorly by the transverse ligament of knee (Makris, Hadidi, & Athanasiou, 2011).

Due to the passage of very thick tendons in the knee joint, there are water cushions called bursa between them (Chatra, 2012).

The bursa in the anterior

Subcutaneous prepatellar bursa

Deep infrapatellar bursa

Subcutaneous infrapatellar bursa

Suprapatellar bursa

The bursa in the lateral

Lateral subtendinous bursa of gastrocnemius

Inferior subtendinous bursa of biceps femoris

Subpopliteal recess

The bursa in the medial

Medial subtendinous bursa of gastrocnemius

Anserine bursa

Semimembranosus bursa (Chatra, 2012)

Arterial Circulation of The Knee Joint.

The arterial circulation of the knee joint is provided by the descending genicular artery, genicular branch of popliteal artery, anterior tibial recurrent artery, descending branch of lateral circumflex femoral artery ((Shim & Leung, 1986)

Sensory Innervation of The Knee Joint

Sensory innervation of the knee joint is provided by the femoral nerve, obturator nerve, tibial nerve, and common fibular nerve (Fonkoué et al., 2019).

Movements of The Knee Joint

Since the knee joint is a special type of gingival joint, it performs flexion and extension movement in the transverse axis and medial and lateral rotation, albeit limited, in the vertical axis. While the last 30-degree foot is in a fixed position on the ground, the hip joint rotates laterally while the knee is medially rotated. Conversely, when the hip joint rotates medially, the knee rotates laterally (Table 1) (Gilleard, Crosbie, & Smith, 2008).

Table 1. Movement of the knee joint

Movement	Muscle	Origin	Insertion	Innervation
Flexion of the knee	Semimembranosus	Ischial tuberosity	Medial condyle of tibia	Tibial nerve (L5-S2)
	Semitendinosus	Ischial tuberosity	Medial condyle of tibia Pes anserinus	Tibial nerve (L5-S2)
	Biceps femoris	Long head: Ischial tuberosity Short head: lateral lip of linea aspera	Head of fibula	Long head: tibial nerve (L5-S2) Short head: common fibular nerve (L5-S2)
	Gracilis	Inferior pubic ramus, ramus of ischium	Medial condyle of tibia Pes anserinus	Obturator nerve (L2-L3)
	Sartorius	Anterior superior iliac spine	Medial condyle of tibia Pes anserinus	Femoral nerve (L2-L3)
	Gastrocnemius	Lateral head: Lateral condyle of femur- Medial head: Medial condyle of femur	Calcaneal tendon	Tibial nerve (S1, S2)
	Plantaris	Lateral epicondyle of femur	Medial border of the calcaneal tendon	Tibial nerve (S1, S2)
	Popliteus	Lateral condyle of femur Arcuate popliteal ligament	Posterior surface of proximal tibia	Tibial nerve (L4-S1)
	Rectus femoris	Anterior inferior iliac spine, supraacetabular groove	Tibial tuberosity via patellar ligament	Femoral nerve (L2-L4)
	Vastus medialis	Medial lip of linea aspera	Tibial tuberosity via patellar ligament	Femoral nerve (L2-L4)
Extension of the knee	Vastus lateralis	Lateral lip of linea aspera	Tibial tuberosity via patellar ligament	Femoral nerve (L2-L4)
	Vastus intermedius	Anterior surface of femoral shaft	Tibial tuberosity via patellar ligament	Femoral nerve (L2-L4)
Lateral rotation of the knee	Biceps femoris	Long head: Ischial tuberosity Short head: lateral lip of linea aspera	Head of fibula	Long head: tibial nerve (L5-S2) Short head: common fibular nerve (L5-S2)
	Gracilis	Inferior pubic ramus, ramus of ischium	Medial condyle of tibia Pes anserinus	Obturator nerve (L2-L3)
	Sartorius	Anterior superior iliac spine	Medial condyle of tibia Pes anserinus	Femoral nerve (L2-L3)
Medial rotation of the knee	Popliteus	Lateral condyle of femur Arcuate popliteal ligament	Posterior surface of proximal tibia	Tibial nerve (L4-S1)
	Semimembranosus	Ischial tuberosity	Medial condyle of tibia	Tibial nerve (L5-S2)
	Semitendinosus	Ischial tuberosity	Medial condyle of tibia Pes anserinus	Tibial nerve (L5-S2)

Test for ACL rupture

Anterior drawer test: This test tests the integrity of the anterior cruciate ligament. The patient flexes the leg 90° while lying on his back. The therapist/doctor stabilizes the patient's ankle with the hip while palpating the joint line with the thumbs. The patient's tibia is pulled forward. An anterior displacement of more than 0.2 cm is helpful in the diagnosis of ACL rupture. While the sensitivity of this test is close to 100% in patients with chronic ACL rupture, the sensitivity of this test is 29% in patients with partial tears or acute ruptures (Figure 1) (Lelli, di Turi, Spenciner, & Dòmini, 2016).

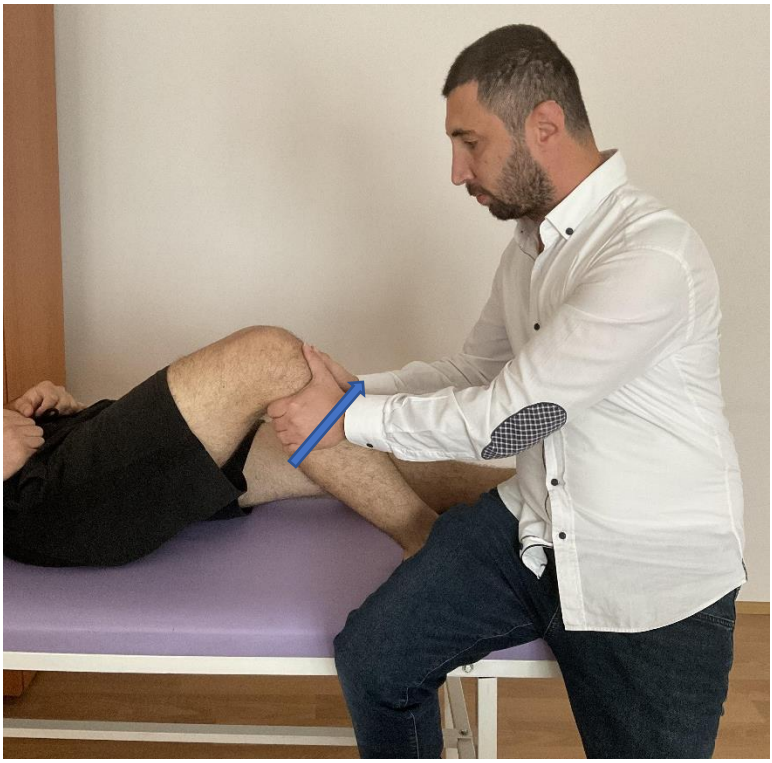


Figure 1. Anterior drawer test for ACL rupture

Lachman Test: The leg of the patient lying on his back is flexed 20-30°. The therapist/doctor places one hand distal to the femur while the other hand places the thumb on the tibial tuberosity with the other fingers palpating the floor of the popliteal fossa and forcing the tibia forward. If a firm-end-feel sensation occurs after forcing the tibia forward, the test is negative, and if a soft-end-feel sensation occurs, ACL rupture u is diagnosed. The sensitivity of the Lachman test was 85% and the reliability was 94% (Benjaminse, et al., 2006).

Pivot Shift Test: 20-30° flat leg lift is performed by grasping the heel of the patient lying on his back. While the patient's heel is turned out and the tibia is internally rotated, valgus stress is applied to the leg from the outside. A clunk from the joint when the leg is pushed into flexion indicates a positive test (Lopomo, Zaffagnini, & Amis, 2013). While this test has a very high specificity (98%), unfortunately its sensitivity (24%) is quite low (Figure 2) (Benjaminse et al., 2006).

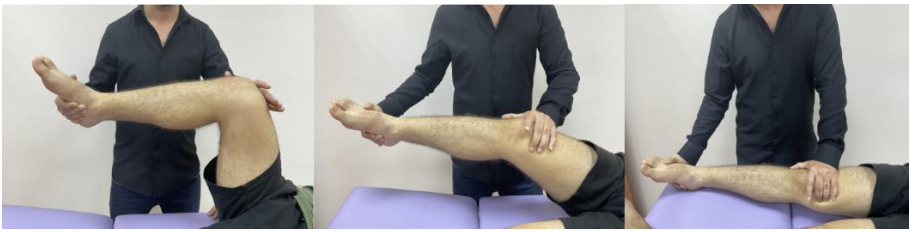


Figure 2. Pivot shift test for ACL rupture

Lever Sign: While the patient is in the supine position, the leg is slightly flexed, and the therapist places her hand in a fist between the heads of the gastrocnemius muscle. The therapist applies a downward push on the quadriceps muscle with the other hand. If the leg comes to the extension position after this push, the test is considered negative. If the leg does not extend after pushing and the femoral condyles descend downward, the test is considered positive and ACL rupture is diagnosed (Lelli et al., 2016) The sensitivity of this test is 64.1%, while the specificity is 92.3% (Gürpinar, Polat, Polat, Çarkçi, & Öztürkmen, 2019).

Test for PCL rupture

Posterior sag sign: The patient flexes the hip 45 degrees and the knee 90 degrees while lying on his back. The patient's foot is in full contact with the table in the resting position. In this position, the tibial tuberosity should be 1 cm ahead. If the tibial tuberosity is displaced backwards, this test can be considered positive, and a diagnosis of PCL rupture can be made. The sensitivity of this test is 79% and the specificity is 88% (Rubinstein et al., 1994).

Posterior drawer test: The patient flexes the hip 45 degrees and the knee 90 degrees while lying on his back. The patient's foot is in full contact with the table in the resting position. The therapist/doctor palpate the joint with both hands. The tibia is pushed backwards. If the tibia recedes more than 6 mm or there is a soft-end-feel, the test is considered positive, and a preliminary diagnosis of PCL rupture can be made. The sensitivity of this test is 90% and the specificity is 99% (Figure 3) (Feltham & Albright, 2001)

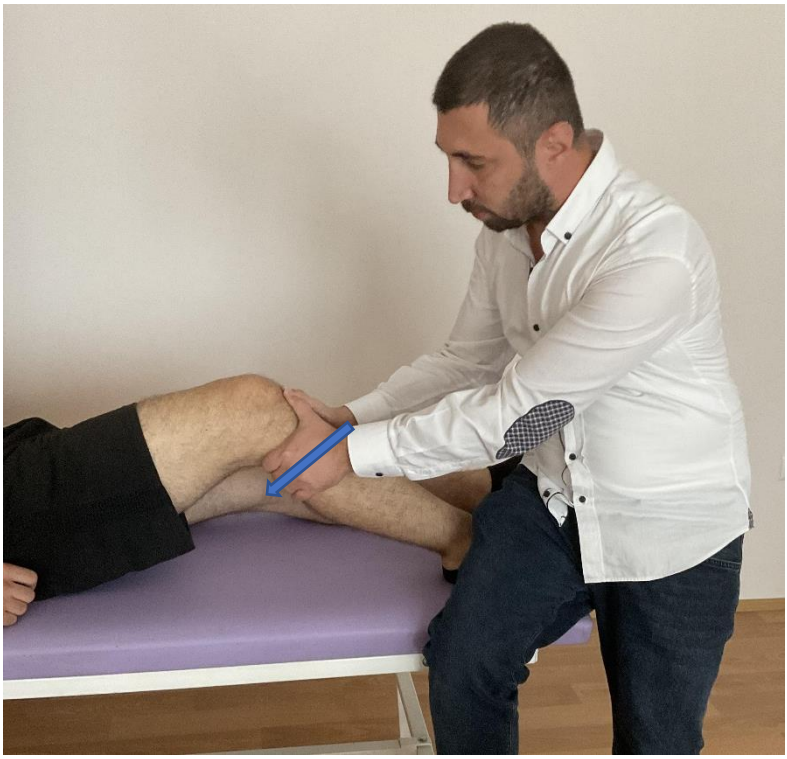


Figure 3. Posterior drawer test for PCL rupture

Quadriceps active test: In the supine position, the patient flexes the hip 45 degrees and the knee 90 degrees. The patient's foot is in full contact with the table in the resting position. The therapist/doctor stabilizes the patient's ankle. The patient is asked to contract the quadriceps muscle. While no significant displacement is observed in patients with intact PCL, the tibia is pulled anterior to the femur in patients with PCL rupture. The sensitivity of this test is 54% and the specificity is 97% (Figure 4) (Kieser, Savage, & Sharplin, 2019)

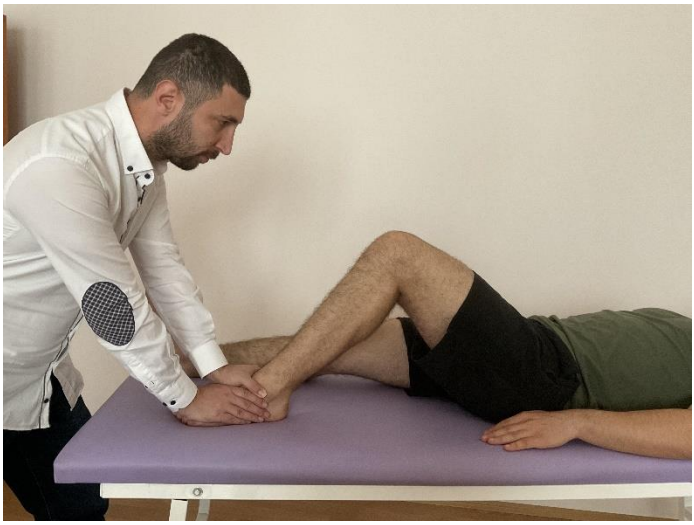


Figure 4. Quadriceps active test for PCL rupture

Test for collateral ligaments

Varus stress test: This test is done with the knee flexed at 0 degrees and 20 degrees. Test for 0 degrees knee flexion: The patient lies in the supine position. The therapist grips the patient's ankle laterally with one hand while placing the other hand on the inside of the upper leg. The therapist forces the patient's leg to varus with the hand holding the patient's ankle. A greater than normal opening (comparable to the unaffected lower extremity) indicates a lateral collateral ligament (LCL) tear. The test for 20-degree knee flexion: The same test is tested with the knee at 20 degrees of flexion. While testing for LCL tear is checked with the knee locked test, the test performed with the knee at 20 degrees of flexion indicates additional lateral meniscus damage to the LCL tear. The sensitivity of this test has been reported as 25% (Figure 5) (Malanga, Andrus, Nadler, & McLean, 2003).

Figure 5. Varus stress test for LCL rupture

Valgus stress test: This test is done with the knee flexed at 0 degrees and 20 degrees. The patient is positioned similarly to the varus position. Test for 0 degrees knee flexion: The therapist/doctor grips the patient's ankle medially with one hand while placing the other hand on the laterally of the upper leg. The patient's leg is forced into valgus. Greater than normal opening (comparable to unaffected lower extremity) medial to the knee joint or pain indicates a positive test. Test for 20 degrees knee flexion: This time, the patient's leg is flexed to 20 degrees and the test is repeated. Similarly, excessive opening or pain in the medial knee joint compared to the opposite extremity indicates that the test is positive. If only Test 1 is positive, it indicates the medial collateral ligament (MCL) tear, if test 2 with test 1 is also positive, it indicates an additional medial meniscus or ACL tear to the MCL tear. The sensitivity of this test has been reported as 66% and specificity as 60% (Figure 6) (Karbach & Elfar, 2017).

Figure 6. Valgus stress test for MCL

Appley's test for collateral ligaments: The patient is placed in the prone position. The knee is flexed 90 degrees. The patient's foot is plantar flexion, and the therapist applies upward traction from the ankle and rotates the leg medially-laterally. With the traction effect, the meniscuses are eliminated. Pain in lateral rotation indicates damage to the MCL, and pain in medial rotation indicates damage to the LCL (Figure 7).

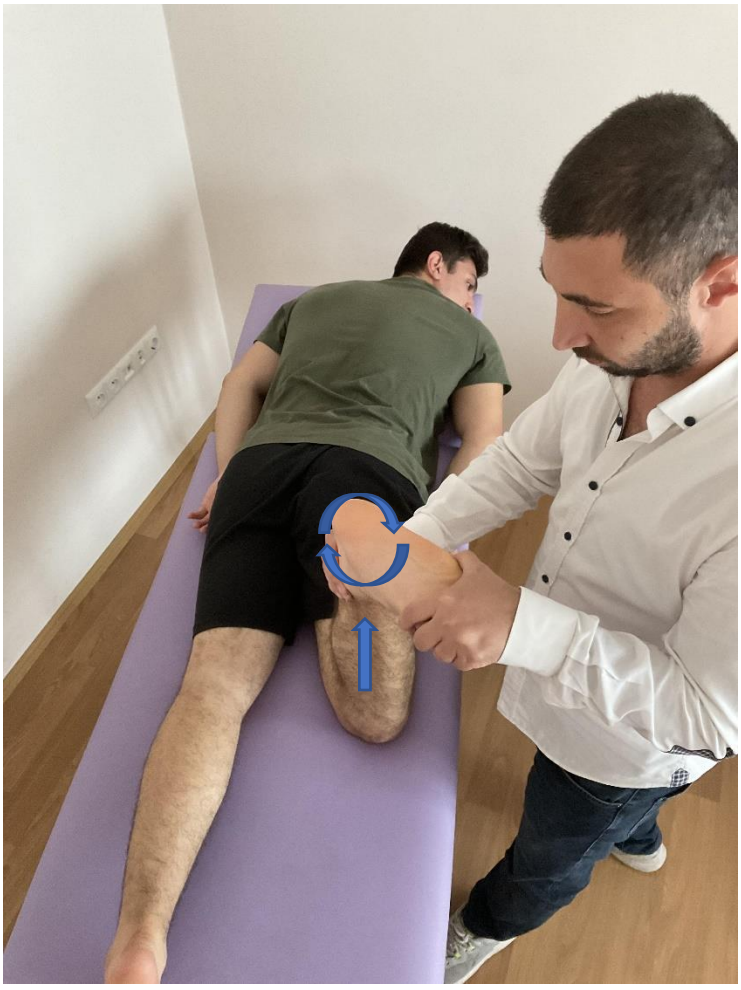


Figure 7. Appley's test for meniscuses

Test for meniscuses

Mc Murray Test for medial meniscus: The patient is placed in the supine position. The therapist puts one hand on the patient's foot and the other on the popliteal fossa. With hip flexion, the knee is brought to full flexion. The therapist brings his hand from the popliteal fossa to the lateral part of the knee joint. The therapist applies valgus stress by forcing the tibia into internal rotation with his hand on the heel. The tested leg is brought into extension. Different angulation, clicking sound and locking sensation in the knee joint are evaluated. If these findings are present, the test is considered positive and medial meniscus damage is determined.

Figure 8. Mc Murray test for MCL

Mc Murray Test for lateral meniscus: The patient is placed in the supine position. The therapist puts one hand on the patient's foot and the other on the popliteal fossa. With hip flexion, the knee is brought to full flexion. The therapist brings his hand from the popliteal fossa to the medial part of the knee joint. The therapist applies varus stress by forcing the tibia into external rotation with his hand on the heel. The tested leg is brought into extension. Different angulation, clicking sound and locking sensation in the knee joint are evaluated. If these findings are present, the test is considered positive and lateral meniscus damage is determined. The sensitivity of both tests is 70%, the specificity is 71% (Hegedus, Hasselblad, Goode, & Mccrory, 2007).

Appley's test for meniscuses: The patient is placed in the prone position. The knee is flexed 90 degrees. The therapist presses the patient's ankle with his hand and rotates the leg medially-laterally. Pain, locking or click sound lateral rotation indicates damage to in the medial meniscus, and the same

findings in medial rotation indicate damage to the lateral meniscus. The sensitivity of this test is 60%, the specificity is 70% (Hegedus et al., 2007).

Thesaly-Test: In this test, the patient stands on. The therapist supports the patient by holding their hands. The patient flexes the non-injured knee and holds it in the air. It flexes the injured leg to 20 degrees. The patient has 3 times medial lateral rotation of the tibia. Pain, locking or click sound lateral rotation indicates damage to in the medial meniscus, and the same findings in medial rotation indicate damage to the lateral meniscus. The sensitivity of this test is 80%, the specificity is 91% (Karachalios et al., 2005).

Knee distraction mobilization

Patient position: The patient hangs her legs while sitting on the treatment table. The thigh touches the bed 5 cm behind the popliteal fossa.

Therapist position: The therapist grasps the medial and lateral sides of the proximal tibia with his hands facing the patient.

Stabilization: Stabilization is provided by body weight.

Mobilization: The therapist applies a distal distraction to the tibia with both hands (Figure 9).

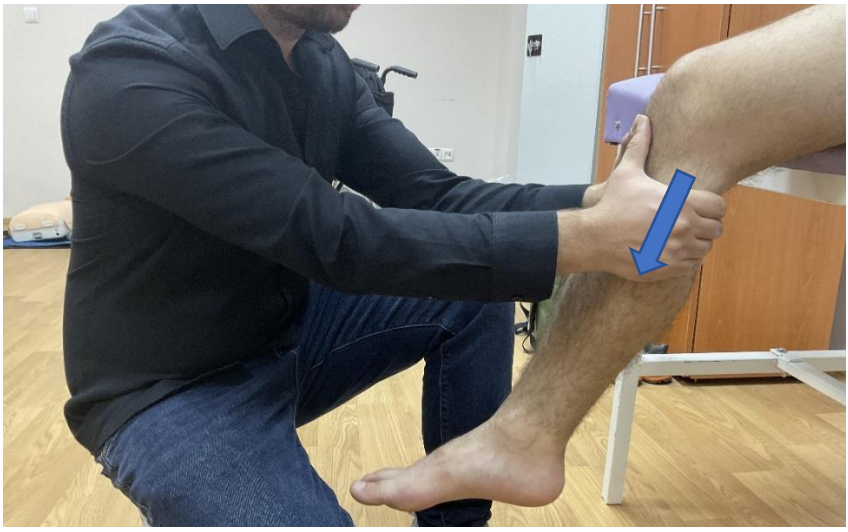


Figure 9. Knee distraction mobilization

Knee flexion mobilization

Aim: Increasing the knee flexion angle.

Patient position: The patient hangs her legs while sitting on the treatment table. The thigh touches the bed 5 cm behind the popliteal fossa. The patient can hold the bed with his hands. The patient flexes the leg.

Therapist position: While facing the patient, the therapist places one hand on the distal tibia and the other on the proximal tibia.

Mobilization: The therapist slides the tibia dorsally with the hand proximal to the tibia (Figure 10).

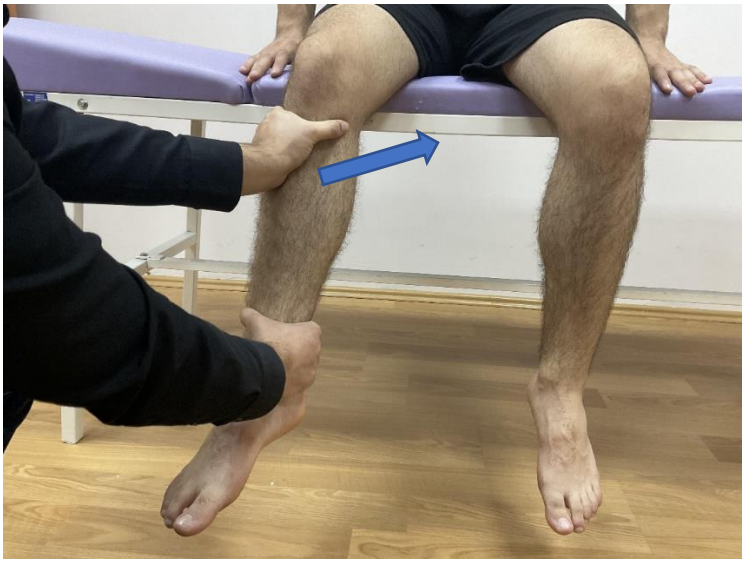


Figure 10. Knee flexion mobilization

Knee extension mobilization

Aim: Increasing the knee extension angle.

Patient position: The patient lies in the prone position with his legs out of the bed.

Therapist position: The therapist is positioned between the patient's legs. The therapist places one hand on the anterior aspect of the distal aspect of leg and the other hand on the posterior aspect of the leg proximal.

Mobilization: The therapist slides the tibia from ventral to dorsal with his hand on the proximal aspect of leg (Figure 11).

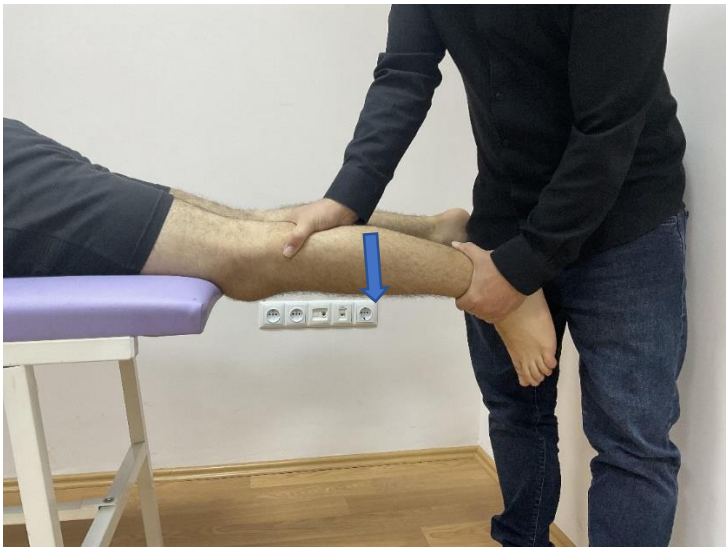


Figure 11. Knee extension mobilization

Medial roll glide

Aim: This technique is used to reduce the limitation of the medial capsule of the knee joint.

Patient position: The knee of the patient lying on his side with his leg in 30 degrees of flexion is supported by a pillow. The other leg is flexed 60 degrees from the hip and knee.

Therapist position: The therapist grasps the ankle with one hand and the lower knee joint with the other hand.

Mobilization: Valgum stress is applied by forcing the knee joint to external rotation (Figure 12).

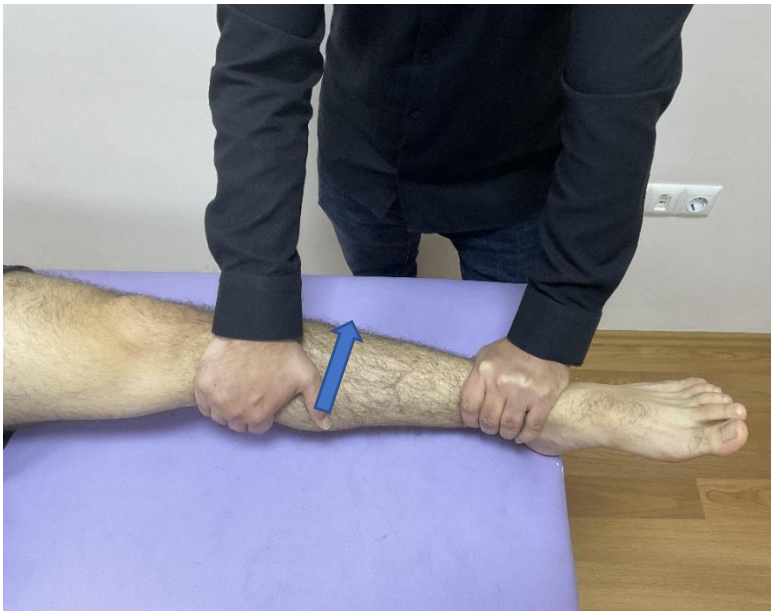


Figure 12. Medial roll glide

Lateral roll glide

Aim: This technique is used to reduce the limitation of the lateral capsule of the knee joint.

Patient position: The knee of the patient lying on his side with his leg in 30 degrees of flexion is supported by a pillow. The other leg is flexed 60 degrees from the hip and knee.

Therapist position: The therapist grasps the ankle with one hand and the lower knee joint with the other hand.

Mobilization: Varus stress is applied by forcing the knee joint to internal rotation (Figure 13).

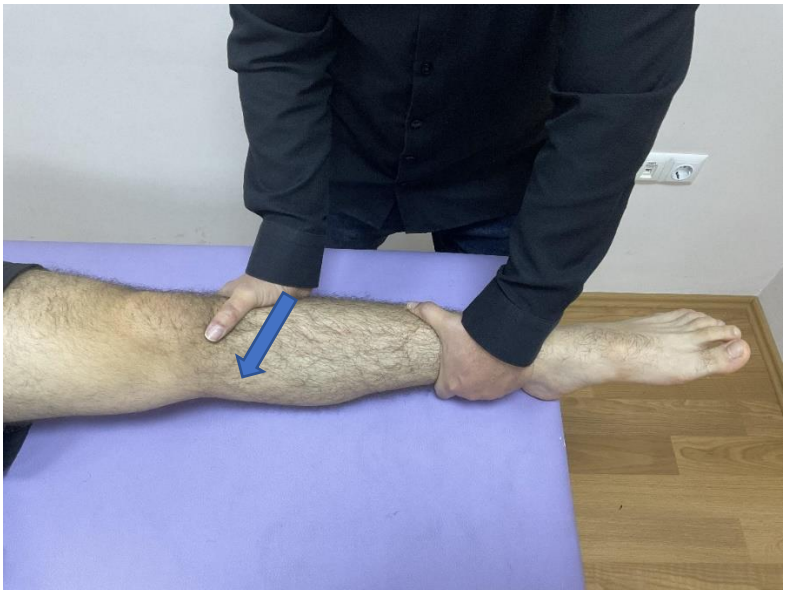


Figure 13. Lateral roll glide

REFERENCES

Andrews, K., Lu, A., Mckean, L., & Ebraheim, N. (2017, December 1). Review: Medial collateral ligament injuries. *Journal of Orthopaedics*, Vol. 14, pp. 550–554. Reed Elsevier India Pvt. Ltd. https://doi.org/10.1016/j.jor.2017.07.017

Beaufils, P., & Pujol, N. (2017, December 1). Management of traumatic meniscal tear and degenerative meniscal lesions. Save the meniscus. *Orthopaedics and Traumatology: Surgery and Research*, Vol. 103, pp. S237–S244. Elsevier Masson SAS. https://doi.org/10.1016/j.otsr.2017.08.003

Benjaminse, A., Gokeler, A., & van der Schans, C. P. (2006). Clinical diagnosis of an anterior cruciate ligament rupture: A meta-analysis. *Journal of Orthopaedic and Sports Physical Therapy*, Vol. 36, pp. 267–288. Movement Science Media. https://doi.org/10.2519/jospt.2006.2011

Bennett 2021. (n.d.).

Chatra, P. S. (2012, February 1). Bursae around the knee joints. *Indian Journal of Radiology and Imaging*, Vol. 22, pp. 27–30. Georg Thieme Verlag. https://doi.org/10.4103/0971-3026.95400

Eymard, F., & Chevalier, X. (2016, July 1). Inflammation of the infrapatellar fat pad. *Joint Bone Spine*, Vol. 83, pp. 389–393. Elsevier Masson SAS. https://doi.org/10.1016/j.jbspin.2016.02.016

Fam, L. P. D., Fruheling, V. M., Pupim, B., Ramos, C. H., de Moura, M. F. A., Namba, M., … Filho, E. S. (2013). Oblique popliteal ligament – an anatomical study. *Revista Brasileira de Ortopedia (English Edition)*, *48*(5), 402–405. https://doi.org/10.1016/j.rboe.2012.07.010

Feltham, G. T., & Albright, J. P. (n.d.). *THE DIAGNOSIS OF PCL INJURY: LITERATURE REVIEW AND INTRODUCTION OF TWO NOVEL TESTS*.

Filbay, S. R., & Grindem, H. (2019, February 1). Evidence-based recommendations for the management of anterior cruciate ligament (ACL) rupture. *Best Practice and Research: Clinical Rheumatology*, Vol. 33, pp. 33–47. Bailliere Tindall Ltd. https://doi.org/10.1016/j.berh.2019.01.018

Fonkoué, L., Behets, C., Kouassi, J. É. K., Coyette, M., Detrembleur, C., Thienpont, E., & Cornu, O. (2019). Distribution of sensory nerves supplying the knee joint capsule and implications for genicular blockade and radiofrequency ablation: an anatomical study. *Surgical and Radiologic Anatomy*, *41*(12), 1461–1471. https://doi.org/10.1007/s00276-019-02291-y

Fox, A. J. S., Bedi, A., & Rodeo, S. A. (2012). The Basic Science of Human Knee Menisci: Structure, Composition, and Function. *Sports Health*, *4*(4), 340–351. https://doi.org/10.1177/1941738111429419

Freeman, M. A. R., & Pinskerova, V. (2003). The movement of the knee studied by magnetic resonance imaging. *Clinical Orthopaedics and Related Research*, *410*, 35–43. Lippincott Williams and Wilkins. https://doi.org/10.1097/01.blo.0000063598.67412.0d

Gilleard, W., Crosbie, J., & Smith, R. (2008). A longitudinal study of the effect of pregnancy on rising to stand from a chair. *Journal of Biomechanics*, *41*(4), 779–787. https://doi.org/10.1016/j.jbiomech.2007.11.015

Gürpinar, T., Polat, B., Polat, A. E., Çarkçi, E., & Öztürkmen, Y. (2019). Diagnostic Accuracy of Lever Sign Test in Acute, Chronic, and Postreconstructive ACL Injuries. *BioMed Research International*, *2019*. https://doi.org/10.1155/2019/3639693

Hegedus, E. J., Hasselblad, V., Goode, A., & Mccrory, D. C. (2007). Physical examination tests for assessing a torn meniscus in the knee: A systematic review with meta-analysis. *Journal of Orthopaedic and Sports Physical Therapy*, Vol. 37, pp. 541–550. Movement Science Media. https://doi.org/10.2519/jospt.2007.2560

John, R., Dhillon, M. S., Syam, K., Prabhakar, S., Behera, P., & Singh, H. (2016). Epidemiological profile of sports-related knee injuries in northern India: An observational study at a tertiary care centre. *Journal of Clinical Orthopaedics and Trauma*, *7*(3), 207–211. https://doi.org/10.1016/j.jcot.2016.02.003

Kane, P. W., Cinque, M. E., Moatshe, G., Chahla, J., DePhillipo, N. N., Provencher, M. T., & LaPrade, R. F. (2018). Fibular Collateral Ligament: Varus Stress Radiographic Analysis Using 3 Different Clinical Techniques. *Orthopaedic Journal of Sports Medicine*, *6*(5). https://doi.org/10.1177/2325967118770170

Karachalios, T., Hantes, M., Zibis, A. H., Zachos, V., Karantanas, A. H., & Malizos, K. N. (2005). *COPYRIGHT © 2005 BY THE JOURNAL OF BONE AND JOINT SURGERY, INCORPORATED Diagnostic Accuracy of a New Clinical Test (the Thessaly Test) for Early Detection of Meniscal Tears*. Retrieved from www.jbjs.org

Karbach, L. E., & Elfar, J. (2017, February 1). Elbow Instability: Anatomy, Biomechanics, Diagnostic Maneuvers, and Testing. *Journal of Hand Surgery*, Vol. 42, pp. 118–126. W.B. Saunders. https://doi.org/10.1016/j.jhsa.2016.11.025

Kawashima 2021. (n.d.).

Kieser, D. C., Savage, E., & Sharplin, P. (2019). *Case Report A Positive Quadriceps Active Test, without the Quadriceps Being Active*.

Lelli, A., di Turi, R. P., Spenciner, D. B., & Dòmini, M. (2016). The "Lever Sign": a new clinical test for the diagnosis of anterior cruciate ligament rupture. *Knee Surgery, Sports Traumatology, Arthroscopy*, *24*(9), 2794–2797. https://doi.org/10.1007/s00167-014-3490-7

Lopomo, N., Zaffagnini, S., & Amis, A. A. (2013, April 1). Quantifying the pivot shift test: A systematic review. *Knee Surgery, Sports Traumatology, Arthroscopy*, Vol. 21, pp. 767–783. Springer Verlag. https://doi.org/10.1007/s00167-013-2435-x

Loudon, J. K. (2016). BIOMECHANICS AND PATHOMECHANICS OF THE PATELLOFEMORAL JOINT. In *The International Journal of Sports Physical Therapy* | (Vol. 11).

Makris, E. A., Hadidi, P., & Athanasiou, K. A. (2011, October). The knee meniscus: Structure-function, pathophysiology, current repair techniques, and prospects for regeneration. *Biomaterials*, Vol. 32, pp. 7411–7431. https://doi.org/10.1016/j.biomaterials.2011.06.037

Malanga, G. A., Andrus, S., Nadler, S. F., & McLean, J. (2003, April 1). Physical examination of the knee: A review of the original test description and scientific validity of common orthopedic tests. *Archives of Physical Medicine and Rehabilitation*, Vol. 84, pp. 592–603. W.B. Saunders. https://doi.org/10.1053/apmr.2003.50026

Pache, S., Aman, Z. S., Kennedy, M., Gilberto, B. ;, Nakama, Y., Moatshe, G., … Philippon, S. (2018). CURRENT CONCEPTS REVIEW Posterior Cruciate Ligament: Current Concepts Review. In *Arch Bone Jt Surg* (Vol. 8). Retrieved from http://abjs.mums.ac.irtheonlineversionofthisarticleabjs.mums.ac.ir

Rubinstein, R. A., Donald Shelbourne, K., Mccarroll, J. R., Vanmeter, C. D., & Rettig, A. C. (n.d.). *The Accuracy of the Clinical Examination in the Setting of Posterior Cruciate Ligament Injuries*.

Russell, F., Zhu, Y., Hey, W., Vaidyanathan, R., & Ellison, P. (2018). A biomimicking design for mechanical knee joints. *Bioinspiration and Biomimetics*, *13*(5). https://doi.org/10.1088/1748-3190/aad39d

Shim 2012. (n.d.).

Song, Y., Xiong, Y., Chen, W., Zuo, F., Tan, L., Yao, J., … Wu, Y. (2018). Sectional Anatomy and Three-Dimensional Visualization of the Posterolateral Complex of the Knee Joint Based on Undeformed High-Resolution Sectional Anatomical Images. *Anatomical Record*, *301*(10), 1764–1773. https://doi.org/10.1002/ar.23926

Steinmetz, S., Brügger, A., Chauveau, J., Chevalley, F., Borens, O., & Thein, E. (2020, January 15). Practical guidelines for the treatment of patellar fractures in adults. *Swiss Medical Weekly*, Vol. 150, p. w20165. NLM (Medline). https://doi.org/10.4414/smw.2020.20165

Vaienti, E., Scita, G., Ceccarelli, F., & Pogliacomi, F. (1885). *Understanding the human knee and its relationship to total knee replacement*. https://doi.org/10.23750/abm.v88i2

CHAPTER 6

CRISPR/Cas9 TECHNOLOGY: A POWERFUL GENOME EDITING TOOL FOR CANCER TREATMENT

Asst. Prof. Dr. Sumeyya Deniz AYBEK[1]
PhD. Kubra SAHIN[2]
MSc. Suheyla Pınar CELIK[3]

[1] Ordu University, Faculty of Medicine, Department of Medical Biology, Ordu, Turkey. sumeyyadenizaybek@odu.edu.tr, Orcid ID: 0000-0001-9957-5485
[2] Tokat Gaziosmanpasa University, Faculty of Medicine, Department of Medical Biology, Tokat, Turkey. kubra944@hotmail.fr, Orcid ID: 0000-0001-9870-0176
[3] Gazi University, Faculty of Sciences, Department of Biology, Ankara, Turkey. pinarsuheylacelik@hotmail.com, Orcid ID: 0000-0001-9315-9261

INTRODUCTION

Cancer is an extremely heterogeneous disease where the 'one-size-fits-all' approach of molecular characterization might be inappropriate for an effective therapeutic outcome (Bhat et al., 2022). Due to heterogeneity among patients and tumors, standard cancer treatments, such as chemotherapy, surgery, and radiotherapy, suitable for only a small subset of the cancer patients. This genetic variability of tumors contributes greatly to the development of field of personalized medicine (Krzyszczyk et al., 2018). Clustered regularly interspaced short palindromic repeats (CRISPR) and CRISPR-associated proteins (Cas) form the CRISPR-Cas system has emerged as a flexible and powerful tool for RNA-guided genome editing (Sander and Joung, 2014). The CRISPR systems are prokaryotic antiviral defense mechanism used by prokaryotic organisms to protect themselves from plasmids or viruses (Sander and Joung, 2014; Singh et al., 2015). Understanding how genomic level alterations, cellular adaptations and changes to the environmental drive the cancer formation, progression and treatment response in individual patients is essential for developing new and improved treatment and diagnosis of the disease. The CRISPR system has high importance on our understanding of cancer biology and genetic disease and continues to drive new science discoveries that promise in helping accelerate treatments for deadly diseases such as cancer (Katti et al., 2022). CRISPR/Cas9 technologies have been widely used to study drug-resistance mechanisms, identify disease-specific drug target, develop biomarkers, discover noncoding sequences, and establish tumor models, which are pivotal for developing targeted drugs needed for optimal cancer therapy (Bhat et al., 2022).

In the first part of this chapter, we have described in detail the CRISPR/Cas system. In the second part of this chapter, we focused on CRISPR/Cas9 genome editing technology in cancers research. Finally, we discuss the side effects and safety of CRISPR/Cas9 mediated therapy.

1.CRISPR/Cas SYSTEM

Archaea and bacteria have evolved RNA mediated adaptive immune systems called CRISPR/Cas that provides organisms protection against both plasmids and viruses (Jinek et al., 2012). The vast majority of bacterial species contain the CRISPR system that provides a great source of functional diversity for modulation of gene expression (Katti et al., 2022). CRISPR is highly regular structure: short unique sequences, also known as spacers, are interspersed with highly conserved palindromic repeats (Haft et al., 2005; Lier et al., 2015). The CRISPR/Cas locus typically are composed of an operon of cas genes and a CRISPR array that are flanked on one side by an AT-rich sequence, also known as the leader sequence, and usually contain a transcription promoter (Butiuc-Keul et al., 2022; Mosterd and Moineau, 2020). In 1987, CRISPR was first recognized in Escherichia coli by Japanese researchers (Ishino et al., 1987). The actual function of this specific DNA repeat regions remained unclear until the mid-2000s. In the early 2000s, the discovery of highly sequence similarity between sequences of plasmids and viruses and the spacer regions of CRISPRs shed light on the functions of CRISPR as a RNA mediated adaptive immune system. At the same time, some researchers have identified a strong relationship between the CRISPR, Cas, and the genes that encode proteins involved in the DNA repair process (Ishino et al., 2018). As a result of comparative genomic analyzes, it was found that CRISPR and Cas proteins work together in a similar way to the eukaryotic RNA interference mechanism (RNAi), protecting prokaryotic cells against invading plasmids and phages (Ishino et al., 2018; Makarova et al., 2006).

The CRISPR/Cas systems are currently classified into two main classes based on the organization style of their effector complex and the structural variation of the Cas genes (Li et al., 2020; Shmakov et al., 2017). Class 1 is classifed into type I, III and IV, also subdivided into further subtypes. Class 2 is classifed into types II, V and VI that has been divided into several subtypes (Chaudhuri et al., 2022). Until today, 6 types of CRISPR/Cas systems and at least 29 subtypes have been identified and the list is rapidly expanding. Although these systems have significant differences at the molecular level between the different types, they use similar processes (Li et al., 2020; Mosterd and Moineau, 2020). The CRISPR/Cas effector complex is required for the maturation of primary CRISPR RNAs (crRNAs), as well as interference and

degradation of foreign nucleic acids. The class 1 CRISPR/Cas systems contain multiprotein effector complexes, are most common in prokaryotes, comprising about 90% of all identified CRISPR/Cas locus. The class 2 CRISPR/Cas systems consist of only a single effector protein (Shmakov et al., 2017). The most preferred subtype of CRISPR/Cas systems is the type II CRISPR/Cas9, specifically the Cas9 variant isolated from *Streptococcus pyogenes* (SpCas9). The relatively simple architecture of the CRISPR/Cas9 technology makes it attractive for use in the new generation gene editing tools (Li et al., 2020; Shmakov et al., 2017).

1.1.Action Mechanism

The CRISPR/Cas mechanism is typically divided into main three stages. Spacer acquisition is the first stage of this mechanism, referred to as 'immunisation' or 'adaptation'. The second stage is named as 'crRNA biogenesis' or 'expression' and the last stage as 'DNA (or RNA) interference' (Guzmán et al., 2021; Makarova and Koonin, 2015). In the spacer acquisition stage, short genomic segments of foreign DNA are acquired and integrated into the CRISPR array in the host genome as a new spacer (Karvelis et al., 2013). The new acquired spacers act as genetic records of past infections that are passed to each new generation of the host (Jiang and Doudna, 2015). During the crRNA biogenesis stage, crRNAs are transcribed into long primary transcripts (pre-crRNAs) from CRISPR loci, which are then processed into mature crRNAs. Similar to the eukaryotic RNAi system, the CRISPR/Cas system uses small guide RNAs (crRNA) to recognise complementary sequences in foreign DNA (Guzmán et al., 2021). Finally, in the interference stage, crRNAs combine with Cas proteins into an effector ribonucleoprotein (RNP) complex which recognizes target DNA sequence for degradation, thereby preventing proliferation and propagation of plasmids and phages (Jiang and Doudna, 2015).

1.2. CRISPR/Cas9 Applications In Genetic Disorders

Gene targeting techniques give scientists the ability to manipulate the genome at specific sites. The recently developed CRISPR/Cas9 system is easy and fast, has enabled the efficient genetic manipulation of endogenous genes in a broad range of important cell types and organisms in biomedical fields as well as a potential new therapeutic avenue for human genetic diseases. (Sander

and Joung, 2014; Singh et al., 2015). Many genes have been found to be effective in the pathogenesis of genetic diseases (Baghini et al., 2022). Such targeting of defective endogenous gene can be accomplished by the CRISPR/Cas9 technology both in vitro and in vivo. In vitro gene therapy involves isolating the target cells with mutated genes from the body, and manipulated by programmable nucleases to correct the mutated genes in vitro then the correct sequences of the target genes can be transplanted directly into the patient (Jayarajan et al., 2021). In recent years, the CRISPR/Cas9 technology has exhibited promising potential to diagnose and treat Duchenne muscular dystrophy (Young et al., 2016), β-thalassemia (Pavani et al., 2021), hemophilia A and B (Han et al., 2022), central nervous system associated diseases (Torregrosa et al., 2021), cystic fibrosis (Ensinck et al., 2021), fragile X syndrome disorders (Xie et al., 2016), and Tay–Sachs diseases (Leal et al., 2022).

2. CRISPR/Cas9 IN CANCERS RESEARCH

Cancer is the most common genetic disease, and it is characterized by genomic instability and structural alterations occur during cancer initiation and progression (Zhang and Zhang, 2020). This disease is one of the main causes of human death worldwide due to its high incidence and mortality rates and imposes a serious economic burden (Chen et al., 2022). There are four main types of conventional cancer treatments: radiotherapy, chemotherapy, surgery, and immunotherapy as single treatments or in combination. Surgery can be used when a tumor is solid and located in a certain area of the body. However, many cancers have the ability to metastasize and in these cases stronger treatment approaches such as chemotherapy and radiotherapy are needed (Krzyszczyk et al., 2018). In treating cancers, chemotherapy has been widely used modality as single treatment or in combination with radiotherapy. These treatment approaches involve high doses of drugs and radiation in order to destroy or damage tumor cells and can also damage to healthy cells (Debela et al., 2021; Krzyszczyk et al., 2018). Cancer is a complex disease that can arise from different genetic causes and may express different genes in one people with cancer than in another. Due to heterogeneity among patients and tumors, conventional cancer treatments, such as surgery, chemotherapy, radiotherapy, and immunotherapy, suitable for only a small subset of the cancer patients. This

heritable variability of tumors contributes greatly to the development of the field of personalized and precision medicine (Krzyszczyk et al., 2018).

Understanding how genomic level alterations, cellular adaptations and changes to the environmental drive the cancer formation, progression and treatment response in individual patients is essential for developing new and improved treatment and diagnosis of the disease (Katti et al., 2022). In recent years, tumor suppressor genes, oncogenes, genes involved in therapeutic resistance to radiation and chemotherapy, and metabolism-related genes have been specifically targeted and edited with the CRISPR gene editing technology to prevent cancer development and progression (Baghini et al., 2022). CRISPR/Cas9 technologies have been widely used to study drug-resistance mechanisms, identify disease-specific drug target, develop biomarkers, discover noncoding sequences, and establish tumor models, which are pivotal for developing targeted drugs needed for optimal cancer therapy (Bhat et al., 2022).

2.1. CRISPR/Cas9 Base Editing In Cancer

Genetic studies has shown that gene mutations are associated with the occurrence, progression, treatment, and prognosis of cancer (Chen et al., 2022). Base editing is a new therapeutic genome editing tool that uses RNA-guided CRISPR-associated nucleases to generates point mutations in target DNA or RNA at specific positions without making direct double-stranded DNA breaks (DSBs). In cells, base editing can change genomic DNA sequence or mRNA transcript abundance (Rees and Liu, 2018). Base editors include two main groups: adenine base editors, which induces A to G substitutions; and cytosine base editors, which induces the conversion of C to T (Anzalone et al., 2020). The introduction of point mutations into endogenous genes by CRISPR/Cas9-derived base editing enables the study of their effects on cancer formation. (Annunziato et al., 2020). CRISPR/Cas9-based base editing technology is a potent approach for studying tumor associated genomic variants and enable the development of personalized medicine in the future (Bhat et al., 2022).

2.2. CRISPR/Cas9 Mediated Drug Targets

In oncology, an important goal of personalized medicine is to identify new candidate drug targets dependent on individual’s genomic variants. The development of CRISPR/Cas9 technology has facilitated the manipulation of

genes to recognize and validate critical proteins for therapeutic targeting ex vivo and in vivo (Bhat et al., 2022). In recent years, CRISPR/Cas9-based in vivo and in vitro research of some types of cancer have revealed potential therapeutic targets and new treatment approaches. For example, CD38 is a glycoprotein that has attracted particular attention in cancer therapy, and daratumumab, is an anti-CD38 monoclonal antibody, is used for treatment of multiple myeloma. However, its role in non-hematological malignancies is not clear. Bu et al. (2018) found that CRISPR/Cas9 mediated knockout of CD38 in a lung adenocarcinoma cell line reduced tumor formation and suggested that anti-CD38 therapy may have potential in the treatment of lung cancer (Bu et al., 2018). Selection of the new drug candidate is a crucial step for the development of the most effective treatment strategy. A candidate molecule and/or protein cannot be considered as a valuable therapeutic target based only on the expression level of molecular target (Liu et al., 2019). For example, increased expression of the forkhead-box transcription factor C1 (FOXC1) was identified as a biomarker of breast cancer. However, Mott et al. (2018) found that FOXC1 may not be a promising drug target for breast cancer-like cell line (generated by CRISPR/Cas9) (Mott et al., 2018). These studies highlight the importance of in vivo research based on the CRISPR/Cas9 system in the validation of new drug targets and their reliability.

2.3. CRISPR/Cas9 In Cancer Immunotherapy

Many studies have found that long-term exposure to high levels of tumor antigen leads to a state of "Exhausted" T cells. Tumors provide a source of persistent antigen while avoiding clearance, and promote T cell exhaustion (Dimitri et al., 2022). In recent years, immunotherapy has attracted increasing attention, which can be defined as the use of a person's own immune system in tumor treatment (Akkın et al., 2021). Immunotherapy improves our immune system's ability to fight cancer. Some types of immunotherapy, including adoptive cell transfer (ACT) therapy and immune checkpoint inhibitors, are successful in sustained clinical response, but these treatment approaches are not equally effective in all subsets of cancer patients (Zhang and Zhang, 2020). These treatments are also used as a combined treatment with other traditional therapeutic approaches (Bhat et al., 2022). Checkpoint inhibitors have been an effective treatment to sustain T cell function, and inhibitory receptors such as

programmed cell death 1 (PD-1) is being tested in clinical studies to ameliorate or prevent T cell exhaustion (Dimitri et al., 2022). ACT therapy utilize genetically engineered T cells that target private neoantigens to eliminate cancer cells and have shown sustained clinical efficacy. This therapy is comprised of T-cell receptor (TCR)-engineered T cells and chimeric antigen receptor (CAR)-T cells, which have made significant advances in the treatment of malignant tumors (Zhang and Zhang, 2020). CAR-T cell therapy have dramatically transformed the hematological malignancies treatment (Mueller et al., 2022). Recently, CAR insertion into the T cell receptor alpha constant gene (TRAC) locus of primary human T cells using viral vectors and/or CRISPR/Cas9 technology was shown to generate CAR-T cells (Kath et al., 2021). Applications of viral vectors are the current gold standards for manufacturing of clinical-grade CAR-T cells. However, the use of viral vectors is complex and costly, and resulting in heterogeneous CAR expression. Consequently, applications of viral vectors may cause the total CAR signal within a cell to exceed or fall below the ideal level (Kath et al., 2021; Mueller et al., 2022).

Recent approaches in CRISPR/Cas9 genome editing enables targeting of the CAR transgene to a spesific genomic region to more strongly control CAR expression. In addition, CRISPR/Cas9 mediated multiplex knockout of immune checkpoint inhibitors enhance CAR T-cell function and persistence, which may permit for circumvention of T cell intrinsic and extrinsic resistance mechanisms operative in different types of cancer (Dimitri et al., 2022). Mueller et al. (2022) generated anti-disialoganglioside (GD2) CAR-T cells using CRISPR/Cas9 system for GD2+ solid tumors. They found that anti-GD2 CAR-T cells induce regression of solid tumor in a human neuroblastoma xenograft mouse model (Mueller et al., 2022). Jung and colleagues (2018) used CRISPR/Cas9 to knock out diacylglycerol kinase (DGK) to enhance T cell function by increasing CD3 signaling in CAR-T cells. They reported that knockout of DGK demonstrably enhances the effector functions of CAR-T cells, caused important regression of U87MGvIII glioblastoma tumors (Jung et al., 2018).

3. CRISPR/Cas9 Clinical Trials

The number of CRISPR/Cas9 clinical trials is growing significantly every year. However, many of the current clinical trial processes are still in early phases, which focus on the side effects and safety of CRISPR/Cas9 mediated therapy. Current clinical trials are ongoing in seven areas: cancers, blood disorders, diabetes, inherited eye disease, protein-folding disorders, infectious disease, and inflammatory disease. In the cancer area, search words CRISPR/cas9 and tumor reveal 33 clinical trials, of which three were terminated in the US and two were completed in China, 5 have been suspended or withdrawn 7 are unknown, and 16 are recruiting (ClinicalTrials.gov).

In a Chinese clinical trial (2016), a patient with lung cancer became the first human in the world to be treated with a CRISPR/cas9-based therapy (NCT02793856). In this clinical study, PD-1 knockout edited T cells generated via CRISPR/Cas9 were transferred to the patient (Cyranoski, 2016). In 2020, Lu et al. reported the results from a first-in-human phase I clinical study in 12 patients with non-small-cell lung cancer. In this clinical trial, PD-1 knockout engineered T cells generated via CRISPR/Cas9 were also transferred to the patients. They found that the clinical trial was safe to use and had minor side effects like rash, fever, and fatigue. Moreover, they found that off-target mutation frequencies were low at 18 candidate sites, and suggested that clinical application of CRISPR/Cas9 technology is usually safe and feasible (Lu et al., 2020). In the US, the first CRISPR/Cas9-mediated clinical study combined PD-1 and CAR-T cancer immunotherapy, using CRISPR/Cas9 to manipulate three genes. In the phase I study, Stadtmauer and colleagues aimed to test the safety and feasibility of clinical trial in one with metastatic sarcoma and two with advanced relapsed myeloma. There were acceptable side effects associated with the manipulated T cells and the CRISPR/Cas9-mediated clinical trial was safe to administer. The manipulated T cells engrafted in all three patients at stable levels for the nine months of the clinical trial. Biopsies of tumor and bone marrow on the three patients demonstrated that T cells were able to to reach the sites of tumors. Off-target mutation frequencies were low. However, chromosomal translocations were determined in vitro during T cell manufacturing process, and the percentage of T cells with mutations decreased after infusion into patients (Stadtmauer et al., 2020). These preliminary clinical trials have demonstrate that CRISPR/cas9-based therapy may be a promising

option for patients: the side effects are tolerable, it appears to be fairly and feasible, and the therapy does not tend to cause strong immune responses.

4. CONCLUSION

Cancer is an extremely heterogeneous disease where the 'one-size-fits-all' approach of molecular characterization might be inappropriate for an effective therapeutic outcome. Therefore, specialized treatment approaches are needed for better prognostic outcomes of cancer patients. The CRISPR/Cas9 technology has been heavily used to establish tumor models, study drug-resistance mechanisms, identify disease-specific drug target, develop biomarkers, and discover noncoding sequences. Highly efficient changes of gene expression and genome sequence through the use of a CRISPR gene editing technology will undoubtedly transform biomedical research and enable the development of new molecular treatment options for cancer. However, there are some problems that influence the effectiveness of the CRISPR/Cas9 system which must be solved before effective in vivo gene therapy, such as continuous activity of Cas9, off-target effects, uncontrollable DNA repair, low efficiency of low efficiency of CRISPR/Cas9-based gene knock-in, current delivery systems, and pre-existing adaptive immunity (Lino et al., 2018). Preliminary clinical trials have shown that multiplexed CRISPR/Cas9 technology is safe and feasible. In patients, long-term persistence of the edited T cells showes that preexisting adaptive immunity to Cas9 do not appear to present any barrier to the CRISPR/Cas9-based genome editing.

REFERENCES

Akkın, S., Varan, G., & Bilensoy, E. (2021). A Review on Cancer Immunotherapy and Applications of Nanotechnology to Chemoimmunotherapy of Different Cancers. Molecules (Basel, Switzerland), 26(11), 3382. https://doi.org/10.3390/molecules26113382

Annunziato, S., Lutz, C., Henneman, L., Bhin, J., Wong, K., Siteur, B., van Gerwen, B., de Korte-Grimmerink, R., Zafra, M. P., Schatoff, E. M., Drenth, A. P., van der Burg, E., Eijkman, T., Mukherjee, S., Boroviak, K., Wessels, L. F., van de Ven, M., Huijbers, I. J., Adams, D. J., Dow, L. E., … Jonkers, J. (2020). In situ CRISPR-Cas9 base editing for the development of genetically engineered mouse models of breast cancer. The EMBO journal, 39(5), e102169. https://doi.org/10.15252/embj.2019102169

Anzalone, A. V., Koblan, L. W., & Liu, D. R. (2020). Genome editing with CRISPR-Cas nucleases, base editors, transposases and prime editors. Nature biotechnology, 38(7), 824–844. https://doi.org/10.1038/s41587-020-0561-9

Baghini, S. S., Gardanova, Z. R., Abadi, S. A. H., Zaman, B. A., İlhan, A., Shomali, N., Adili, A., Moghaddar, R., & Yaseri, A. F. (2022). CRISPR/Cas9 application in cancer therapy: a pioneering genome editing tool. Cellular & molecular biology letters, 27(1), 35. https://doi.org/10.1186/s11658-022-00336-6

Bhat, A. A., Nisar, S., Mukherjee, S., Saha, N., Yarravarapu, N., Lone, S. N., Masoodi, T., Chauhan, R., Maacha, S., Bagga, P., Dhawan, P., Akil, A. A., El-Rifai, W., Uddin, S., Reddy, R., Singh, M., Macha, M. A., & Haris, M. (2022). Integration of CRISPR/Cas9 with artificial intelligence for improved cancer therapeutics. Journal of translational medicine, 20(1), 534. https://doi.org/10.1186/s12967-022-03765-1

Bu, X., Kato, J., Hong, J. A., Merino, M. J., Schrump, D. S., Lund, F. E., & Moss, J. (2018). CD38 knockout suppresses tumorigenesis in mice and clonogenic growth of human lung cancer cells. Carcinogenesis, 39(2), 242–251. https://doi.org/10.1093/carcin/bgx137

Butiuc-Keul, A., Farkas, A., Carpa, R., & Iordache, D. (2022). CRISPR-Cas System: The Powerful Modulator of Accessory Genomes in Prokaryotes. Microbial physiology, 32(1-2), 2–17. https://doi.org/10.1159/000516643

Chaudhuri, A., Halder, K., & Datta, A. (2022). Classification of CRISPR/Cas system and its application in tomato breeding. TAG. Theoretical and applied genetics. Theoretische und angewandte Genetik, 135(2), 367–387. https://doi.org/10.1007/s00122-021-03984-y

Chen, X. Z., Guo, R., Zhao, C., Xu, J., Song, H., Yu, H., Pilarsky, C., Nainu, F., Li, J. Q., Zhou, X. K., & Zhang, J. Y. (2022). A Novel Anti-Cancer Therapy: CRISPR/Cas9 Gene Editing. Frontiers in pharmacology, 13, 939090. https://doi.org/10.3389/fphar.2022.939090

Cyranoski D. (2016). Chinese scientists to pioneer frst human CRISPR trial. Nature, 535:476–7. https://doi.org/10.1038/nature.2016.20302

Debela, D. T., Muzazu, S. G., Heraro, K. D., Ndalama, M. T., Mesele, B. W., Haile, D. C., Kitui, S. K., & Manyazewal, T. (2021). New approaches and procedures for

cancer treatment: Current perspectives. SAGE open medicine, 9, 20503121211034366. https://doi.org/10.1177/20503121211034366

Dimitri, A., Herbst, F., & Fraietta, J. A. (2022). Engineering the next-generation of CAR T-cells with CRISPR-Cas9 gene editing. Molecular cancer, 21(1), 78. https://doi.org/10.1186/s12943-022-01559-z

Ensinck, M., Mottais, A., Detry, C., Leal, T., & Carlon, M. S. (2021). On the Corner of Models and Cure: Gene Editing in Cystic Fibrosis. Frontiers in pharmacology, 12, 662110. https://doi.org/10.3389/fphar.2021.662110

Guzmán, N. M., Esquerra-Ruvira, B., & Mojica, F. J. M. (2021). Digging into the lesser-known aspects of CRISPR biology. International microbiology : the official journal of the Spanish Society for Microbiology, 24(4), 473–498. https://doi.org/10.1007/s10123-021-00208-7

Haft, D. H., Selengut, J., Mongodin, E. F., & Nelson, K. E. (2005). A guild of 45 CRISPR-associated (Cas) protein families and multiple CRISPR/Cas subtypes exist in prokaryotic genomes. PLoS computational biology, 1(6), e60. https://doi.org/10.1371/journal.pcbi.0010060

Han, J. P., Kim, M., Choi, B. S., Lee, J. H., Lee, G. S., Jeong, M., Lee, Y., Kim, E. A., Oh, H. K., Go, N., Lee, H., Lee, K. J., Kim, U. G., Lee, J. Y., Kim, S., Chang, J., Lee, H., Song, D. W., & Yeom, S. C. (2022). In vivo delivery of CRISPR-Cas9 using lipid nanoparticles enables antithrombin gene editing for sustainable hemophilia A and B therapy. Science advances, 8(3), eabj6901. https://doi.org/10.1126/sciadv.abj6901

Ishino, Y., Shinagawa, H., Makino, K., Amemura, M., and Nakata, A. (1987). Nucleotide Sequence of the Iap Gene, Responsible for Alkaline Phosphatase Isozyme Conversion in Escherichia coli, and Identification of the Gene Product. J. Bacteriol. 169, 5429–5433. doi:10.1128/jb.169.12.5429-5433.1987

Ishino, Y., Krupovic, M., & Forterre, P. (2018). History of CRISPR-Cas from Encounter with a Mysterious Repeated Sequence to Genome Editing Technology. Journal of bacteriology, 200(7), e00580-17. https://doi.org/10.1128/JB.00580-17

Jayarajan, V., Kounatidou, E., Qasim, W., & Di, W. L. (2021). Ex vivo gene modification therapy for genetic skin diseases-recent advances in gene modification technologies and delivery. Experimental dermatology, 30(7), 887–896. https://doi.org/10.1111/exd.14314

Jiang, F., & Doudna, J. A. (2015). The structural biology of CRISPR-Cas systems. Current opinion in structural biology, 30, 100–111. https://doi.org/10.1016/j.sbi.2015.02.002

Jinek, M., Chylinski, K., Fonfara, I., Hauer, M., Doudna, J. A., & Charpentier, E. (2012). A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity. Science (New York, N.Y.), 337(6096), 816–821. https://doi.org/10.1126/science.1225829

Jung, I. Y., Kim, Y. Y., Yu, H. S., Lee, M., Kim, S., & Lee, J. (2018). CRISPR/Cas9-Mediated Knockout of DGK Improves Antitumor Activities of Human T Cells.

Cancer research, 78(16), 4692–4703. https://doi.org/10.1158/0008-5472.CAN-18-0030

Karvelis, T., Gasiunas, G., Miksys, A., Barrangou, R., Horvath, P., & Siksnys, V. (2013). crRNA and tracrRNA guide Cas9-mediated DNA interference in Streptococcus thermophilus. RNA biology, 10(5), 841–851. https://doi.org/10.4161/rna.24203

Kath, J., Du, W., Thommandru, B., Turk, R., Amini, L., Stein, M., Zittel, T., Martini, S., Ostendorf, L., Wilhelm, A., Akyuz, L., Rehm, A., Höpken, U.E., Pruß, A., Künkele, A., Jacobi, A.M., Volk, H-D., Schmueck-Henneresse, M., Reinke, P., Wagner, D.L. (2021). Fast, efficient and virus-free generation of TRAC-replaced CAR T cells. bioRxiv, 2021.02.14.431017; doi: https://doi.org/10.1101/2021.02.14.431017

Katti, A., Diaz, B. J., Caragine, C. M., Sanjana, N. E., & Dow, L. E. (2022). CRISPR in cancer biology and therapy. Nature reviews. Cancer, 22(5), 259–279. https://doi.org/10.1038/s41568-022-00441-w

Krzyszczyk, P., Acevedo, A., Davidoff, E. J., Timmins, L. M., Marrero-Berrios, I., Patel, M., White, C., Lowe, C., Sherba, J. J., Hartmanshenn, C., O'Neill, K. M., Balter, M. L., Fritz, Z. R., Androulakis, I. P., Schloss, R. S., & Yarmush, M. L. (2018). The growing role of precision and personalized medicine for cancer treatment. Technology, 6(3-4), 79–100. https://doi.org/10.1142/S2339547818300020

Leal, A. F., Cifuentes, J., Quezada, V., Benincore-Flórez, E., Cruz, J. C., Reyes, L. H., Espejo-Mojica, A. J., & Alméciga-Díaz, C. J. (2022). CRISPR/nCas9-Based Genome Editing on GM2 Gangliosidoses Fibroblasts via Non-Viral Vectors. International journal of molecular sciences, 23(18), 10672. https://doi.org/10.3390/ijms231810672

Li, H., Yang, Y., Hong, W., Huang, M., Wu, M., & Zhao, X. (2020). Applications of genome editing technology in the targeted therapy of human diseases: mechanisms, advances and prospects. Signal transduction and targeted therapy, 5(1), 1. https://doi.org/10.1038/s41392-019-0089-y

Lier, C., Baticle, E., Horvath, P., Haguenoer, E., Valentin, A. S., Glaser, P., Mereghetti, L., & Lanotte, P. (2015). Analysis of the type II-A CRISPR-Cas system of Streptococcus agalactiae reveals distinctive features according to genetic lineages. Frontiers in genetics, 6, 214. https://doi.org/10.3389/fgene.2015.00214

Lino, C. A., Harper, J. C., Carney, J. P., & Timlin, J. A. (2018). Delivering CRISPR: a review of the challenges and approaches. Drug delivery, 25(1), 1234–1257. https://doi.org/10.1080/10717544.2018.1474964

Liu, B., Saber, A., & Haisma, H. J. (2019). CRISPR/Cas9: a powerful tool for identification of new targets for cancer treatment. Drug discovery today, 24(4), 955–970. https://doi.org/10.1016/j.drudis.2019.02.011

Lu, Y., Xue, J., Deng, T., Zhou, X., Yu, K., Deng, L., Huang, M., Yi, X., Liang, M., Wang, Y., Shen, H., Tong, R., Wang, W., Li, L., Song, J., Li, J., Su, X., Ding, Z., Gong, Y., Zhu, J., … Mok, T. (2020). Safety and feasibility of CRISPR-

edited T cells in patients with refractory non-small-cell lung cancer. Nature medicine, 26(5), 732–740. https://doi.org/10.1038/s41591-020-0840-5

Makarova, K. S., Grishin, N. V., Shabalina, S. A., Wolf, Y. I., & Koonin, E. V. (2006). A putative RNA-interference-based immune system in prokaryotes: computational analysis of the predicted enzymatic machinery, functional analogies with eukaryotic RNAi, and hypothetical mechanisms of action. Biology direct, 1, 7. https://doi.org/10.1186/1745-6150-1-7

Makarova, K. S., & Koonin, E. V. (2015). Annotation and Classification of CRISPR-Cas Systems. Methods in molecular biology (Clifton, N.J.), 1311, 47–75. https://doi.org/10.1007/978-1-4939-2687-9_4

Mosterd, C., & Moineau, S. (2020). Characterization of a Type II-A CRISPR-Cas System in Streptococcus mutans. mSphere, 5(3), e00235-20. https://doi.org/10.1128/mSphere.00235-20

Mott, L., Su, K., & Pack, D. W. (2018). Evaluation of FOXC1 as a therapeutic target for basal-like breast cancer. Cancer gene therapy, 25(3-4), 84–91. https://doi.org/10.1038/s41417-018-0010-9

Mueller, K. P., Piscopo, N. J., Forsberg, M. H., Saraspe, L. A., Das, A., Russell, B., Smerchansky, M., Cappabianca, D., Shi, L., Shankar, K., Sarko, L., Khajanchi, N., La Vonne Denne, N., Ramamurthy, A., Ali, A., Lazzarotto, C. R., Tsai, S. Q., Capitini, C. M., & Saha, K. (2022). Production and characterization of virus-free, CRISPR-CAR T cells capable of inducing solid tumor regression. Journal for immunotherapy of cancer, 10(9), e004446. https://doi.org/10.1136/jitc-2021-004446

Pavani, G., Fabiano, A., Laurent, M., Amor, F., Cantelli, E., Chalumeau, A., Maule, G., Tachtsidi, A., Concordet, J. P., Cereseto, A., Mavilio, F., Ferrari, G., Miccio, A., & Amendola, M. (2021). Correction of β-thalassemia by CRISPR/Cas9 editing of the α-globin locus in human hematopoietic stem cells. Blood advances, 5(5), 1137–1153. https://doi.org/10.1182/bloodadvances.2020001996

Rees, H. A., & Liu, D. R. (2018). Base editing: precision chemistry on the genome and transcriptome of living cells. Nature reviews. Genetics, 19(12), 770–788. https://doi.org/10.1038/s41576-018-0059-1

Sander, J. D., & Joung, J. K. (2014). CRISPR-Cas systems for genome editing, regulation and targeting. Nature biotechnology, 32(4), 347–355. https://doi.org/10.1038/nbt.2842

Singh, P., Schimenti, J. C., & Bolcun-Filas, E. (2015). A mouse geneticist's practical guide to CRISPR applications. Genetics, 199(1), 1–15. https://doi.org/10.1534/genetics.114.169771

Shmakov, S., Smargon, A., Scott, D., Cox, D., Pyzocha, N., Yan, W., Abudayyeh, O. O., Gootenberg, J. S., Makarova, K. S., Wolf, Y. I., Severinov, K., Zhang, F., & Koonin, E. V. (2017). Diversity and evolution of class 2 CRISPR-Cas systems. Nature reviews. Microbiology, 15(3), 169–182. https://doi.org/10.1038/nrmicro.2016.184

Stadtmauer, E. A., Fraietta, J. A., Davis, M. M., Cohen, A. D., Weber, K. L., Lancaster, E., Mangan, P. A., Kulikovskaya, I., Gupta, M., Chen, F., Tian, L., Gonzalez, V. E., Xu, J., Jung, I. Y., Melenhorst, J. J., Plesa, G., Shea, J., Matlawski, T., Cervini, A., Gaymon, A. L., … June, C. H. (2020). CRISPR-engineered T cells in patients with refractory cancer. Science (New York, N.Y.), 367(6481), eaba7365. https://doi.org/10.1126/science.aba7365

Torregrosa, T., Lehman, S., Hana, S., Marsh, G., Xu, S., Koszka, K., Mastrangelo, N., McCampbell, A., Henderson, C. E., & Lo, S. C. (2021). Use of CRISPR/Cas9-mediated disruption of CNS cell type genes to profile transduction of AAV by neonatal intracerebroventricular delivery in mice. Gene therapy, 28(7-8), 456–468. https://doi.org/10.1038/s41434-021-00223-3

Young, C. S., Hicks, M. R., Ermolova, N. V., Nakano, H., Jan, M., Younesi, S., Karumbayaram, S., Kumagai-Cresse, C., Wang, D., Zack, J. A., Kohn, D. B., Nakano, A., Nelson, S. F., Miceli, M. C., Spencer, M. J., & Pyle, A. D. (2016). A Single CRISPR-Cas9 Deletion Strategy that Targets the Majority of DMD Patients Restores Dystrophin Function in hiPSC-Derived Muscle Cells. Cell stem cell, 18(4), 533–540. https://doi.org/10.1016/j.stem.2016.01.021

Xie, N., Gong, H., Suhl, J. A., Chopra, P., Wang, T., & Warren, S. T. (2016). Reactivation of FMR1 by CRISPR/Cas9-Mediated Deletion of the Expanded CGG-Repeat of the Fragile X Chromosome. PloS one, 11(10), e0165499. https://doi.org/10.1371/journal.pone.0165499

Zhang, Y., & Zhang, Z. (2020). The history and advances in cancer immunotherapy: understanding the characteristics of tumor-infiltrating immune cells and their therapeutic implications. Cellular & molecular immunology, 17(8), 807–821. https://doi.org/10.1038/s41423-020-0488-6

CHAPTER 7

COSMETIC GYNECOLOGY

Res. Asst. Ali HÜSEYİNOĞLU[1]
Assoc. Prof. Dr. Deha Denizhan KESKİN[2]
Assoc. Prof. Dr. Seda KESKİN[3]

[1] Ordu University, Faculty of Medicine, Obstetrics and Gynecology Department, Ordu, Turkey dr.huseyinogluali@gmail.com, ORCID ID 0000-0002-6887-1799
[2] Ordu University, Faculty of Medicine, Obstetrics and Gynecology Department, Ordu, Turkey dehadenizhankeskin@gmail.com, ORCID ID 0000-0002-6108-7619
[3] Ordu University, Faculty of Medicine, Obstetrics and Gynecology Department, Ordu, Turkey adesniksek@gmail.com, ORCID ID 0000-0002-5640-4552

INTRODUCTION

Aesthetic operations are dramatically increasing in all fields and related with each body parts. Genital system is also in this increasing trends. When genital aesthetic operations are first started, only the labia minoras are related; today, there are aesthetic operations for the entire genital area. Hyaluronic acid fillers, thread applications, surgical excisions are popular for female external genital system. According to the 2017 Cosmetic Surgery National Data Bank Statistics by the American Society for Aesthetic Plastic Surgery, labiaplasty is the most increasing procedure by 217.3% over the past 5 years (Cosmetic Surgery National Data Bank Statistics).

1.HISTORY OF COSMETIC GYNECOLOGY

1.1. Ancient Ages

The history of genital aesthetics is as old as the history of beauty and goes back to ancient Egypt. For centuries, women have tried to manipulate their genitals through practices such as naming and coloring (Goodman, 2020).

1.2. First Description in Gynecology

François Mauriceau, one of the pioneers of obstetrics, described a patient who was disturbed by the appearance of her genital lips in 1681 in his book titled “The Diseases of Women with Child and Child Bearing” (Mauriceau, 1964).

1.3. First Academic Definition

The first publications on cosmetic and sexual practices for the female genital area belong to the 1970s. Although the desire of women to beautify their genital areas dates back to ancient times, it can be said that cosmetic gynecology practices have developed rapidly in the last 10 years (Schnatz, 2020).

1.4. Cosmetic Gynecology Today

Since the beginning of the 2000s, the widespread use of the internet, the increase in the sharing of pornographic videos and images, the rapidly developing social media culture, the increase in social interest in visuals and the concept of 'comparison race' have increased the interest in genital operations (Mowat et al., 2015).

2.IDEAL VULVA IMAGE

Hodgkinson and Hait described the ideal vulva image in their study in 1984. In this study, they drew attention to the ratio between the labia minora and the labia majora and stated that the labia minora should be smaller than the labia majora. In this aesthetic appearance, the labia minora should be located

symmetrically and not exceeding the labia majora borders (Hodgkinson and Hait, 1984).

3.GENITAL VARIATIONS

Female genital sizes have a fairly wide variation. The most variation in size is observed in the labia minora. The labia minora differs from person to person in terms of thickness and symmetry. The most common cause of labial minor hypertrophy is congenital. It can also be acquired due to exposure to exogenic hormones, topical estrogen use, lymphedema, recurrent dermatitis and myelodysplastic diseases (Kreklau et al, 2018).

Variability of Female Genitalia (Kreklau et al, 2018)

- Width of clitoris 1-22 mm (4.6 mm)
- Length of clitoris 0.5-34 mm (6.8 mm)
- Distance clitoris-urethra 3-65 mm (22.6 mm)
- Introitus opening 6-75 mm (27.9 mm)
- Length of perineum 3-55 mm (21.3 mm)
- Length of labia majora (right and left) 12-180 mm (79.8 mm)
- Length of labia minora (right and left) 2-61 mm (42.6 mm)
- Width of labia minora (right and left) 1-61 mm (13.7 mm)

4. LABIA MINOR HYPERTROPHY CLASSIFICATION

There are different classification systems for the definition of labial minor hypertrophy. In the Franco classification, which is the most widely used classification system, the distance between the most distal end of the labia minora and the base of the labia minora is measured. Accordingly, there are four classes of labial minor dimensions: stage I (>2 cm), stage II (2-4 cm), stage III (4-6 cm) and stage IV (>6 cm) (Franco, 1993).

5.WISHES AND EXPECTATIONS

The patient's wishes and expectations regarding the genital area should be evaluated within the framework of the benefit-harm relationship, and if the patient's complaint is within anatomically normal limits, it should be shared with the patient. The patient should be asked whether she has had a genital aesthetic operation before. During the evaluation of the patient, a psychologist or psychiatrist consultation should be requested first in case of any suspected psychological disorder. No genital aesthetic intervention should be performed on patients who are unsuitable in any respect (Shaw et al., 2013).

6.COSMETIC GYNECOLOGY FROM PAST TO PRESENT

6.1. Past

In the past, female external genital operations were used as reconstructive surgery in cases of congenital genital problems (such as adrenogenital syndrome, ambigius genitale, vaginal agenesis), weakening of genital organs and tissues (such as urinary incontinence, pelvic organ prolapse, vaginal dryness, dyspareunia). Recently, a huge boom has been observed in genital aesthetic operations due to the increasing awareness of external genital organ appearance (Lloyd et al.,2005).

6.2. Present

Today, in cosmetic gynecology, laser applications (vaginal tightening, stress incontinence, prolapse treatments, etc.), surgical correction operations (labiaplasty, perineoplasty, etc.), filler applications (chemical fillings, fat transfer, etc.), botulinum toxin applications (vaginismus, stress incontinence, etc.), liposuction (abdomen, pubis) are more widely used (Kurban, 2020).

The term "female genital cosmetic surgery" is used to describe multiple procedures such as labiaplasty, clitoral head reduction, hymenoplasty, labia major augmentation, vaginoplasty, and G-spot amplification (Schnatz, 2020).

7. PELVIC ORGAN PROLAPSUS

Sagging in the genital organs can occur for different reasons. The most common causes include pregnancy, vaginal delivery, obesity, menopause, weight lifting, heavy-duty occupations, chronic constipation, chronic obstructive pulmonary diseases, neurological disorders, and pelvic organ surgeries (Swift et al., 2001).

The main treatment method applied in genital organ prolapse is surgery. In patients who cannot undergo surgery, measures such as kegel exercises, weight control, smoking cessation, diet changes, and not lifting heavy can be applied. In some special indications, medical treatment and pessary use may also be recommended (Jelovsek et al., 2007).

8. GENITOURINARY MENOPASUE SYNDROME

Genitourinary menopause syndrome (GSM) is the term used to describe a group of symptoms that includes vaginal pain, vaginal dryness, itching, dispharonia, and vaginal fragility, as well as urinary symptoms such as frequent urination, urgency, urinary incontinence, hematuria. Women who complain of GSM symptoms have traditionally been treated with vaginal lubricants, vaginal moisturizers or low-dose vaginal estrogens. In the cosmetic industry, lasers have also been used for collagen remodeling and skin repair (Phillips et al., 2022).

9. AESTHETIC AND COSMETIC SURGERY

- Labiaplasty (Labia minora and labia mimora)
- Hudoplasty (Clitoral Hood Reduction)
- Vaginoplasty (Vaginal tightening or Vaginal rejuvenation)
- Perinoplasty
- Hymenoplasty
- Labia Majora Augmentation
- Others (Puboplasty, Frenuloplasty, Vulvoplasty)

9.1. Labiaplasty

The labia minor and sometimes the labia major require different surgical approaches. Labiaplasty is often used to describe a procedure used to achieve symmetry between the labia minora (Schnatz, 2020).

The purpose of this technique is to eliminate unwanted tissue of the labia minora or labia majora (Schnatz, 2020).

A classical scalpel is generally used for the operation. Today, the frequency of use of applications such as laser and radiofrequency labiaplasty is increasing.

Labium aesthetics can be applied in four main techniques (Eserdağ, 2020).

- Trim or edge resection
- Wedge resection using a V-shaped or Y-shaped incision (applied on large and fleshy labia)
- Z-plasty
- De-epithelization

Complications of this technique include infection, scarring, hypersensitivity or loss of sensation, dyspareunia and wound dehiscence (Eserdağ, 2020).

9.2. Hudoplasty

Hudoplasty (clitoral hood reduction) is the procedure of reducing the excess skin covering the clitoris to normal sizes. The main technique of the procedure is hoodectomy. However, excessive reduction should not be done. In such wrong applications, the head of the clitoris may come forward and is not pleasing to the eye (Eserdağ, 2020).

The purpose of this technique is to improve sexual function by increasing sensitivity and allowing more direct clitoral contact (Eserdağ, 2020).

Usually, this procedure is combined with labioplasty to create labia minora symmetry and prevent clitoral hood sagging. Rarely, there may be excess skin on the clitoral hood (isolated clitoral hood). In this case, a procedure such as labiaplasty should not be added to the surgery (Eserdağ, 2020).

Complications of this technique include infection, scarring, hypersensitivity, hematoma and damage to the glans (Eserdağ, 2020).

9.3. Vaginoplasty

Vaginoplasty, also known as vaginal tightening and vaginal rejuvenation, is an aesthetic method applied to narrow and tighten the vagina. This procedure is usually applied because of the dissatisfied appearance that is present from birth or usually develops after vaginal births (Goodman, 2011).

Vaginoplasty is also demanded by patients due to the feeling of looseness in sexual intercourse. With vaginoplasty applied with appropriate indication, sexual pleasure can be increased by increasing coital friction during sexual intercourse (Goodman, 2011).

Vaginoplasty surgery is technically a surgical procedure in which parts of the vaginal mucosa are excised and the lumen of the vagina is reconstructed. In the laser vaginoplasty method, laser is used to increase vaginal muscle tone, strength and control, and to reduce the inner and outer vaginal diameters (Goodman, 2011).

Vaginoplasty can be performed using many different techniques. (Eserdağ, 2020).

- Anterior colporrhaphy
- Posterior colporrhaphy
- Lateral colporrhaphy
- Rugation restoration
- Energy-based devices

Complications of this technique include infection, dyspareunia, fistula and dehiscence (Eserdağ, 2020).

9.4. Perineoplasty

The perineum is the name given to the area between the entrance of the vagina and the anus. The appearance of the perineum can often deteriorate after vaginal deliveries. After episiotomy, which is frequently applied during childbirth, the incisions do not heal completely and cause irregularity of the perineum (Eserdağ, 2020).

Perineoplasty, which raises and strengthens the perineal area, is an operation to aesthetically correct the perineal area. Healed episiotomy scars may leave a depression or swelling in the perineal region by creating a bad appearance with the procedure. With perineoplasty procedure, an aesthetic appearance is given to the perineal area (Eserdağ, 2020).

Complications of this technique include infection, dyspareunia and dehiscence (Eserdağ, 2020).

9.5. Hymenoplasty

In some religions, cultural roots are given importance to the subject of virginity of unmarried women. Hymenoplasty or hymen suturing is the process of surgically renewing the hymen. The purpose of this technique is to recreate the original state of the hymen (Eserdağ, 2020).

There are basically two types of hymenoplasty methods.

- Permanent hymenoplasty
- Temporary hymenoplasty
- Both technique

Temporary hymenoplasty is the procedure performed 6-7 days before coitus without incision. In this process, hymen remnants can be brought end to end with sutures or inner circular sutures can be tied in the middle. If sexual intercourse occurs shortly after this procedure, the stitches are torn and vaginal bleeding occurs (Kurban, 2020).

In the permanent hymenoplasty method, a mucosal flap taken from the vagina is used. This live flap taken in the flap method is placed in the vaginal opening and the vaginal entrance is narrowed. As with the other method, bleeding with sexual intercourse is observed (Ou et al., 2008).

The main complication of this procedure is wound dehiscence.

9.6. Labia Majora Augmentation

In labia majora augmentation, the labia majora is filled by using plumping agents (hyaluronic acid, etc.) or autologous fat transfer injection (Schnatz, 2020).

The main goal of this procedure is to create a full, symmetric genital look (Eserdağ, 2020).

The most common complication of this operation is palpable fatty cysts (Eserdağ, 2020).

10. AESTHETIC AND COSMETIC INJECTIONS

- G Shot
- O Shot
- Others (Urinary Incontinence, Genital Warts, Recurrent Vaginal Infections, Vulvodynia …)

10.1. G Shot

The G-spot was first described by Ernest Gräfenberg in 1950. This point or area is located on the anterior vaginal wall approximately 5 cm above the

urethral ostium. According to some sources, this 1-2 cm zone is considered erogenous (Grafenberg, 1950).

In the G-shot process, hyaluronic acid fillers or autologous fat transfers are made to this area, which is considered erogenous. With this method, it is aimed to increase the pleasure from sexual intercourse (Ostrzenski, 2011).

10.2. O Shot

O Shot, or 'Orgasm Vaccine', is the application of PRP (Platelet Rich Plasma) to the clitoral complex with a special method. PRP is the plasma part prepared from the person's own blood by centrifugation (Eserdağ, 2020).

PRP contains growth factors and regenerates cells in the area where it is applied. It also increases the blood supply in the tissue. It is thought that the frequency and severity of orgasm during sexual intercourse increase with this method (Eserdağ, 2020).

11. GENITAL WHITENING

Genital darkening, also known as genital hyperpigmentation, has many different genetic and environmental causes. Among the causes of darkening of the color of the external genital area; exposure to ultraviolet rays, solarium use, birth control pills, polycystic ovary syndrome (PCOS), aging, hormonal changes due to pregnancy, laser hair removal, genital waxing, use of tight underwear, smoking. Some systemic diseases (especially insulin resistance) and some chronically used drugs can also cause genital discoloration (Eserdağ, 2020).

In recent years, various laser bleaching technologies have been used to lighten the dark skin color in the vulvar and perianal region. Laser application is an application that suppresses melanin in the genital area. With these genitoanal applications, it is aimed to remove the dark layer in the epidermis. In the treatment of vulvar hyperpigmentation, skin lightening cosmeceuticals and micro dermabrasion treatment can also be applied (Qureshi et al., 2018).

11.1. Fitzpatrick Scale

Skin color was classified by the Fitzpatrick scale, first defined by Thomas Fitzpatrick (Fitzpatrick, 1988).

Fitzpatrick scale (Fitzpatrick, 1988)

Type I

- Skin Color: White; very fair; red or blond hair; blue eyes; freckles
- Characteristics: Always burns, never tans

Type II

- Skin Color: White; fair; red or blond hair; blue, hazel or green eyes
- Characteristics: Usually burns, tans with difficulty

Type III
- Skin Color: Cream white; fair with any eye or hair color; very common
- Characteristics: Sometimes mild burn, gradually tans

Type IV
- Skin Color: Brown; typical Mediterranean Caucasian skin
- Characteristics: Rarely burns, tans with ease

Type V
- Skin Color: Dark Brown; mid-eastern skin types
- Characteristics: Very rarely burns, tans very easily

Type VI
- Skin Color: Black
- Characteristics: Never burns, tans very easily

12. FEMALE GENITAL COSMETIC SURGERY COMPLICATIONS

Women should be informed about the lack of high-quality data supporting the efficacy of genital cosmetic surgery procedures and their potential complications such as pain, bleeding, infection, scarring, adhesions, sensory alteration, dyspareunia, and the need for reoperation (Goodman, 2011).

13. RECOMMENDATIONS OF MAJOR GYNECOLOGICAL SOCIETIES ON FEMALE GENITAL COSMETIC SURGERY

13.1. Royal College of Obstetricians and Gynaecologist (RCOG)

- Fully informed consent/consent must be provided,
- Women should be informed about the variety of normal genital appearance,
- Psychological intervention should be recommended for problems such as body image problems,
- Be aware that surgeons perform procedures that lack a clear evidence base,
- Genital Cosmetic Surgery should not be applied to women and girls under the age of 18 regardless of their approval,
- Women should be informed that there is no reliable evidence regarding the risks and positive effects of Genital Cosmetic Surgery,

- Genital Cosmetic Surgery should not be provided by the National Health Service.

13.2. American College of Obstetricians and Gynecologists (ACOG)

- Genital Cosmetic Surgery is not medically recommended, and there is no documentation on its safety and efficacy.
- Women should be informed about the lack of data supporting the efficacy of Genital Cosmetic Surgery and its possible complications,
- From all women who request Genital Cosmetic Surgery; evaluation of sexual dysfunction, consideration of other non-surgical interventions (eg, counseling) to improve sexual functions,
- Ethical issues related to the marketing of the Genital Cosmetic Surgery should be considered.

13.3. The Society of Obstetricians and Gynaecologists of Canada (SGOC)

- Women should be helped to understand their genital anatomy and respect individual differences,
- A complete medical, sexual and gynecological history should be taken of women who want Genital Cosmetic Surgery, and it should be ensured that there is no significant sexual or psychological dysfunction, and any possibility of coercion or exploitation should not be ignored.
- In addition to counseling focused on normal genital changes, the possibility of undesirable consequences of Genital Cosmetic Surgery should be prioritized,
- Discuss the lack of evidence regarding outcomes for subsequent changes in pregnancy or menopause,
- Explain that there is little evidence to support the Genital Cosmetic Surgery in terms of sexual satisfaction or enhancement of self-image,
- Genital Cosmetic Surgery should not be supported for the development of sexual function and advertising of Genital Cosmetic Surgery should be avoided.
- Adolescent girls should not be offered Genital Cosmetic Surgery,
- Recognize non-medical medical terms such as vaginal rejuvenation, clitoral resurfacing, G-spot enhancement as marketing terms only; therefore they should not be evaluated scientifically.

13.4. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)

- Patients requesting Genital Cosmetic Surgery and the reasons for such a request should be evaluated, sexual counseling should be offered,
- Any surgical procedure that lacks scientific evidence should be abandoned.
- Complication risks should be discussed in detail with women.

REFERENCES

Cosmetic Surgery National Data Bank Statistics. Aesthet Surg J. 2017;37(suppl 2):1-29.

Daşıkan, Z., Kıratlı, D., Erdoğan, M. (2019). Women's Genital Appearance Satisfaction: Genital Cosmetic Surgery. *The Journal of Gynecology - Obstetrics and Neonatology, 16*(4), 238-243.

Eserdag, S. (2020). Genital Estetik Cerrahisindeki İpuçları. Ö. F. Karataş, S. Sarıkaya, S. Eserdağ (Ed.), Cinsel Tıp ve Genital Estetik içinde (s. 217-235). İstanbul: İstanbul Tıp Kitabevi.

Fitzpatrick, T. B. (1988). The validity and practicality of sun-reactive skin types I through VI. *Archives of dermatology*, *124*(6), 869-871.

Franco, T., & Franco, D. (1993). Hipertrofia de ninfas. *J. bras. ginecol*, 163-168.

Goodman, M. P. (2011). Female genital cosmetic and plastic surgery: a review. *The journal of sexual medicine*, *8*(6), 1813-1825.

Grafenberg, E. (1950). The role of the urethra in female orgasm. *Int J Sexol*, *3*(2), 146.

Hodgekinson, D. J., & Hait, G. (1984). Aesthetic vaginal labiaplasty. *Plast Reconstr Surg*, *74*(3), 414-416.

Jelovsek, J. E., Maher, C., &Barber, M. D. (2007). Pelvic organ prolapse. *The Lancet*, *369*(9566), 1027-1038.

Kreklau, A., Vâz, I., Oehme, F., Strub, F., Brechbühl, R., Christmann, C., & Günthert, A. (2018). Measurements of a 'normal vulva'in women aged 15–84: a cross-sectional prospective single-centre study. *BJOG: An International Journal of Obstetrics & Gynaecology*, *125*(13), 1656-1661.

Kurban, D. (2020). Genital Estetik Cerrahi Uygulamalar. Ö. F. Karataş, S. Sarıkaya, S. Eserdağ (Ed.), Cinsel Tıp ve Genital Estetik içinde (s. 197-209). İstanbul: İstanbul Tıp Kitabevi.

Lloyd, J., Crouch, N. S., Minto, C. L., Liao, L. M., &Creighton, S. M. (2005). Female genital appearance: 'normality'unfolds. *BJOG: An International Journal of Obstetrics&Gynaecology*, *112*(5), 643-646.

Mauriceau, F. (1964). *Desmaladiesdesfemmesgrosses et accouchées: Avec la véritable et bonneméthode de lesbienaider dan leursaccouchemensnaturels, et lesmoyens de remédier à tousceuxquisontcontrenature, et auxindispositionsdesenfansnouveau-nés... Paris, Henault, 1668*. Cercledulivreprécieux.

Mowat, H., McDonald, K., Dobson, A. S., Fisher, J., & Kirkman, M. (2015). The contribution of online content the promotion and normalisation of female genital cosmetic surgery: a systematic review of the literature. *BMC women's health*, *15*(1), 1-10.

Shaw, D., Lefebvre, G., Bouchard, C., Shapiro, J., Blake, J., Allen, L., ... &Simmonds, A. (2013). Female genital cosmetic surgery. *Journal of Obstetrics and Gynaecology Canada*, *35*(12), 1108-1112.

Ostrzenski, A. (2011). Cosmetic gynecology in the view of evidence-based medicine and ACOG recommendations: a review. *Archives of gynecology and obstetrics*, *284*(3), 617-630.

Ou, M. C., Lin, C. C., Pang, C. C., &Ou, D. (2008). A cerclage method for hymenoplasty. *Taiwanese Journal of Obstetrics and Gynecology*, *47*(3), 355-356.

Qureshi, A. A., Tenenbaum, M. M., &Myckatyn, T. M. (2018). Nonsurgical vulvovaginal rejuvenation with radiofrequency and laser devices: a literature review and comprehensive update for aesthetic surgeons. *Aesthetic surgery journal*, *38*(3), 302-311

Phillips, C., Hillard, T., Salvatore, S., Cardozo, L., Toozs-Hobson, P., &Royal College of Obstetricians and Gynaecologists. (2022). Laser treatment for genitourinary syndrome of menopause: Scientific Impact Paper No. 72 (July 2022). *BJOG: An International Journal of Obstetrics&Gynaecology*.

RANZCOG Women's Health Committee. (2019). Vaginal 'rejuvenation' and cosmetic vaginal procedures. *Australian and New Zealand Journal of Obstetrics and Gynaecology*.

Schnatz, P., Boardman, L. A., &Committee on Gynecologic Practice. (2020). ACOG committee opinion number 795: elective female genital cosmetic surgery. *Obstetrics and Gynecology*, *135*(1), e36.

Swift, S. E., Pound, T., &Dias, J. K. (2001). Case–control study of etiologic factors in the development of severe pelvic organ prolapse. *International Urogynecology Journal*, *12*(3), 187-192.

CHAPTER 8

INFERTILITY FROM ANCIENT TIMES TO THE PRESENT

Research Assistant Begüm Naz MEYDAN[1]
Associate Professor Seda KESKİN[2]
Associate Professor Deha Denizhan KESKİN[3]

[1] Ordu University, Faculty of Medicine, Obstetrics and Gynecology Department, Ordu, Turkey drbnazmeydan@gmail.com, ORCID ID 0000-0002-9273-9333
[2] Ordu University, Faculty of Medicine, Obstetrics and Gynecology Department, Ordu, Turkey adesniksek@gmail.com, ORCID ID 0000-0002-5640-4552
[3] Ordu University, Faculty of Medicine, Obstetrics and Gynecology Department, Ordu, Turkey dehadenizhankeskin@gmail.com, ORCID ID 0000-0002-6108-7619

1. Introduction

Infertility is a complex disease with medical, psychosocial and economic problems dating back to ancient times with the development of humanity. Worldwide 10-15 % of couples have a problem with fertility. Infertility may occur primary or secondary. Primary infertility is difficulty in getting pregnant in 12 months' despite of regular intercourse. Secondary infertility is difficulty in having a child after a spontaneous pregnancy period.

2. History of Infertility

Infertility has been an important medical and social concern since the beginning of humanity, and until now, the woman has been considered the symbol of fertility. From ancient times to the present, the difficulty of conceiving has been a real problem.

Men and women were considered equal in the Egyptians, and the difficulty of conceiving; unlike other societies, it was not considered as a divine punishment, but as a disease that needed to be diagnosed and treated. There are recorded sources discussing the treatment of gynecological diseases up to 1900 BC. In the sketchy drawings showing the understanding of anatomy of the Egyptians, nearly 100 anatomical terms are mentioned; there are references to the female reproductive system such as uterus, vulva, labia and cervix (Lefebvre, 1952). Accordingly, the goddess responsible for diseases was Sekment, and the doctors were his priests. The roles of the gods in the treatment of childbirth were important (Morice, 1992). The goddess Nephtys; she was the goddess of infertile women. On the other hand, it is seen that male infertility was also discussed in the records of the Egyptians. The Egyptians developed detailed diagnostic methods to be able to tell if a woman was fertile or not. The examinations included that the genitals were in communion with the rest of the body, especially the digestive system. This view, adopted by Hippocrates and many medieval physicians, has remained unchanged for hundreds of years (Labat, 1951).

Although the first sources of Western medicine came from Greece, the real change occurred with Hippocrates and his school. Born in 460 BC, Hippocrates wanted to change the way medicine was practiced in that period, which was close to magic, by developing a medical management system based on rational thinking. Infertility was recognized as a medical problem requiring diagnosis and treatment, so women were not excluded from social status. Hippocrates was aware of infertility problems, he theorized some of its causes, such as;(i) incorrect position of the cervix, (ii) by congenital or after ulcer

healing, softening inside of the cavity, (iii) occlusion of the cervix due to amenorrhea, (iv) excessive menstrual flow (thus unable to fix the seed), (v) uterine prolapse. Hippocrates created many treatment options; when the cervix was closed too tightly, a special mixture of red nitrate, cumin, resin and honey had to be used to open the inner opening. Or, the cervix could be enlarged by placing a hollow lead dilator so that fluid can be administered (Renouard, 1861).

It was the Athenian philosophers who, from the fourth century BC, revolutionized doctors' view of women. Woman is presented in Plato's 'Timaeus' as a 'punished man', a humiliated creature. Uterus was seen as an irrational spirit, the cause of all kinds of diseases. The female emits a substance necessary for fertilization during mating. Both males and females contribute to reproduction. In Aristotle's 'On the Generation of Animals' she lost the female role and turned into a simple reservoir for sperm. Female pleasure was unnecessary for reproduction (Barnes, 1984).

The role of the gods was equally important in Roman times. Priests would march through the city during the Martian feast, whipping the bellies of barren women. One of the greatest obstetricians and gynecologists of antiquity was Soranus, the owner of the only book whose gynecology has inspired us for 1500 years and has survived intact. (AD 98-177) He and many Roman doctors thought that pregnancy occurred after menstruation. The period before menstruation was sterile because the uterus was "overloaded". Galien (130-200 AD) believed that the phases of the moon had an effect on the menstrual cycle. Little progress was made in the treatment of infertility during the Roman era (Eastman, 1991).

In the seventh century, Arabic medicine drew its inspiration largely from the Greeks, especially Hippocrates and Galien. This medical school was created in Baghdad between 750 and 850. For Rhazes, one of the causes of infertility was obesity. According to Ibn Sina, the causes of infertility; regarding the abnormality of the 'sperms' produced by the male or female, there could be masculine or feminine genesis, abnormalities in the genital tract or psychological disturbances (melancholy, anxiety).

In Byzantium and the Middle Ages, little progress was made in the diagnosis and treatment of infertility, and the next major advances came with the Renaissance and discoveries in anatomy. However, in the Middle Ages, it was understood that reproduction was an important necessity for the "continuation of the species". It was accepted that there was no ground for annulment of a marriage. If a couple did not engage in sexual intercourse solely

to reproduce, their fertility would decline. Infertility could also occur as a result of sins such as cheating and blasphemy. Fertility could be healed with fasting and prayer. In the Middle Ages, sterility was a cause for fear, as it was a sign of divine punishment.

The era of scientific progress and advances in modern thought and treatment of infertility is the Renaissance period. It was with Da Vince and others that the female body gradually dissolved and magic and gods were replaced by scientific thought and logic. As for anatomy, Vesale published his famous atlas, Humani Corporis Fabrica, in 1543, which contained the anatomy of the female genital organs. Nine years later, Bartolomeo Eustachio drew the uterus and veins. It was also Bartolomeo who recommended that men put their fingers in the vagina after intercourse to encourage conception. He was the pioneer of the idea of artificial insemination. Berengarius corrected Galien's idea of a bicornuate uterus in 1514 (Morice et al., 1995).

Towards the 1600s, there were important developments by other physicians. Ambroise Pare' introduced the idea of dilating the cervix in the treatment of infertility. Amboise was the first to cut the vaginal septum in an infertile woman. Fallop was a professor at the Padua medical school. He described the tubes with the clitoris, vagina, and placenta. In 1672, De Graaf wrote De Mulierum Organis, in which he refuted Aristotle's theories of fertilization and described ovarian and follicular function. He is remembered for the term De Graaf's follicle, but he made a mistake in interpretation: he considered the follicle as an egg (De Graaf, 1965).

More work was done on infertility in the seventeenth century. François Blondel (1603-1703) stated that weak and well-groomed women are more fertile compared to obese women.

By the eighteenth century, real scientific reasoning began to replace observations. After von Leeuwenhoek invented the microscope in 1677.He described the spermatozoid drawn by Niklass under the microscope.

In 1707 Martin Naboth published De Sterilitate on infertility. He mentioned tube obstructions and sclerosis as causes of infertility. In the study named The Seats and Causes of Diseases published in 1769; It was stated by Morgani that abnormalities in the vagina or external genitalia, uterine aplasia, follicular absence or agenesis may be the etiological cause (Novak, 1950)

In 1752, Smellie was the first to conduct experiments and develop protocols that explain the fertilization process and some of them are inaccurate. Despite all the advances in medicine, Infertility was seen as female infertility, and it was rare to consider the possibility of the male being infertile. Despite

the advances in medicine in the Age of Enlightenment, there were still real uncertainties. Women were a constant source of attention; but women were not strong enough and were considered too sensitive. Thus, they were removed from public and professional life and allowed to live an unfree life under pressure indoors. Although there has been progress in the study of infertility, because of a woman's vulnerability, the woman was automatically at fault when the couple was infertile.

One of the pioneers of research on infertility in the 19th century Marion Sims (1813-1883), one of the head doctors of American gynecology, published 'Clinical Notes on Uterine Surgery with Special Reference to the Management of the Sterile Condition' (Sims, 1866). Sims stated in his study that cervical stenosis causes dysmenorrhea and infertility. So for the treatment of infertility, he recommended dilating the cervix with an incision or using bougies. On the other hand, uterine malposition also has an effect on infertility; in these, he was in favor of using manual treatment rather than surgery. The best time for fertility was considered the first 10 days after menstruation. Sims successfully concluded artificial insemination during this period. He emphasized that the quality of sperm plays an important role under the microscope (Sims, 1866).

In the etiology of tubal obstruction and infertility, gonococci were described by E. Noeggerath in 1872. In 1891, Murray developed the idea of using thyroid extract to treat infertility in 1891. The first practical methods of artificial insemination were described in 1899 by Ilya Ivanovich Ivanoff (Ivanoff, 1922). Ascheim and Zondek isolated prolan B using the urine of pregnant women (Ascheim and Zondek, 1928). They were able to stimulate and induce ovulation using gonadotropins. Rubin diagnosed tubal obstructions using the tubal insufflation test (Rubin, 1920).

In the nineteenth century and the first part of the twentieth century, more contributions were made to the diagnosis and physiopathology of infertility, thanks to scientific progress with a rational approach. Great progress has also been made in infertility treatments. Three main lines used in planning treatment were clearly established: tube surgery, ovulation stimulation, and medically assisted reproduction.

On November 1, 1939, Gregory Pincus succeeded in artificial insemination on the first animal. The first results of artificial insemination in humans were recorded by Guttmacher (1943), Stoughton (1948) and Kohlberg (1953a; 1953b). The idea of artificial insemination in humans only became popular after the availability and availability of donor sperm. For many years, indications for homologous artificial insemination were only physiological and

psychological dysfunctions such as retrograde ejaculation, vaginismus, hypospadias and impotance (Guttmacher, 1943); (Stoughton,1948); (Kohlberg,1953).

An American pioneer in sperm freezing, Dr. Jerome K. Sherman developed a simple method for preserving human sperm using glycerol, and in 1953 the first successful human pregnancy was reported with artificial insemination using frozen spermatozoa.

First in-vitro fertilization (IVF) baby in England in 1978 by Steptoe and Edwards was born, followed by an in vitro, sister was born in 1981(Steptoe and Edward, 1978). That same year, the first IVF baby in the US was born at Eastern Virginia Medical School in Norfolk, Virginia.

3. Infertility in Today and Its Causes

According to the definition made by the World Health Organization, infertility is a disease of the male or female reproductive system, which is defined as the inability to achieve pregnancy despite regular and unprotected sexual intercourse for 12 months or longer (WHO, 2018).

Infertility covers a spectrum of reproductive disorders that includes secondary infertility, women who become pregnant without medical attention, and women who need medical treatment to become pregnant (Zegers-Hochschild et al., 2017). Infertility impress millions of people of reproductive age and their families and communities globally. Estimates suggest that 48 million couples and 186 million people around the world are living with infertility (Masceranhans et al, 2012); (Boivin et al, 2007); (Rutstein and Shah , 2004).

Numerous causes of female infertility have been identified in the literature. Among the ovulatory-endocrine disorders, hypogonadotropic hypogonadism dysfunction due to pituitary or hypothalamic diseases, functional hypothalamic amenorrhea, hyperprolactinemia dysfunction because of hypothalamic or pituitary diseases, pharmacological interventions, overweight, polycystic ovary syndrome and other causes such as cirrhosis, chronic kidney disease, vitamin D deficiency, hyperthyroidism and hypothyroidism have been indicated. In addition, it is known that tubal and uterine pathologies as well as endometriosis may cause female infertility (Venturella et al., 2019).

When infertile couples are evaluated, the prevalence of male factor is around 35%. Reproductive anamnesis, spermiograme (semen analysis) is the first test for evaluating an infertile couple (Odisho et al. 2014)Azospremia

which is no sperm in analysis, may be reason of retrograde ejaculation; in that condition, ürine analysis contain motile sperm. Obstructive azospermia is absence of sperm in ejaculate due to transport dysfunction of sperm in male ducts. One of the reasons of obstructive azospermia is congenital deficiency of bilateral vas deferens. This should prompt evaluation of cystic fibrosis transmembrane conductance regulator, the protein absent in patients with cystic fibrosis. The most common cause of non-obstructive azospermia is primary testicular failure. Testesterone levels and FSH(folicule stimulating hormone) levels shoul be studied (van der Steeg JW et al.,2011).

According to Machen and Sandlow , the causes of male infertility can be categorized into pre-testicular and post-testicular causes. Among the pre-testicular causes are hypogonadotropic hypogonadism, elevated prolactin, pharmacological interventions, idiopathic hypogonadotropic hypogonadism, Kallmann syndrome, varicocele, cryptorchidism, testicular cancer, ionizing radiation, chemotherapy, genetic azoospermia/oligospermia, testicular injuries, primary ciliary dyskinesia, antisperm antibodies and lifestyle factors such as exposure to heat, preferred type of underwear, length of mobile phone use, smoking and obesity have been mentioned in their study. In the same study, the absence of vas deferens, Young's Syndrome, EjDO/Seminal Vesicle dysfunction, nerve injuries, certain medications such as alpha-1 antagonists and antipsychotics, erectile dysfunction, hypospadias, chordee and certain synthetic lubricants are mentioned as the post-testicular causes of male infertility (Machen and Sandlow, 2020).

World Health Organization Lower Limits of Normal Semen Parameters (van der Steeg JW et al.,2011)

pH	7.2–7.8
Volume	1.5 cc
Total count	39 million
Concentration	≥15 Milllion sperm/mL(<15 million sperm/mL indicates oligozoospermia)
Motility	≥40% Forward progression (<40% forward progression indicates asthenozoospermia)
Morphology	≥4% Normalforms (by Kruger criteria42) (<4% normally formed sperm indicates teratospermia)
White blood cell count	<1 Million/µL

Values are based on samples from men who had fathered a pregnancy in the previous year and taken after 2 to 7 days of abstinence. Values represent the fifth percentile. A diagnosis of an "abnormal" semen analysis should only be made after a repeat analysis is performed, at least 1 month later

3.1. Anovulation

Twenty-five percent of female infertility is due to ovulation disorders. According to the World Health Organization, ovulatory disorders are divided into four classes;

- Hypogonadotropic hypogonadal anovulation: ie, hypothalamic amenorrhea
- Normogonadotropic normoestrogenic anovulation: ie polycystic ovary syndrome (PCOS)
- Hypergonadotropic hypoestrogenic anovulation: that is, premature ovarian failure
- Hyperprolactinemic anovulation: ie pituitary adenoma

Hypothalamic amenorrhea or functional hypothalamic amenorrhea (FHA) is associated with eating disorders and excessive exercise resulting in decreased hypothalamic GnRH secretion (Santoro et al., 1986).

PCOS; It is the most commonly associated condition of normogonadotropic normoestrogenic anovulation. PCOS is seen in 80 to 85% of anovulatory patients and PCOS affects 8% of all women of reproductive age (Hull, 1987). PCOS diagnosis with 2 out of 3 Rotterdam criteria (ROTTERDAM ESHRE-ASRM , 2004);

- Oligoovulation/anovulation
- Clinical manifestations of hyperandrogenism and/or serological elevations of androgens
- Polycystic ovaries shown by ultrasound

It is thought to cause infertility with dysfunction in the development of the dominant follicle. The pathophysiology behind PCOS and infertility is not fully understood; abnormal pulsatility of GnRH was accepted as the possible underlying cause (Fauser and Van, 1997).

Age-related premature ovarian failure and ovarian resistance are in the class of hypergonadotropic hypoestrogenic anovulation. Environmental factors are associated with decreased follicular amount and smoking is considered the most important of these. As the rate of smoking increases, fertility and the number of follicles decrease. As a result of the increase in cigarette use, an increase is also observed in early menopause (Westhoff et al., 2000).

The presence of hypergonadotropic hypogonadism before the age of 40 is defined as primary ovarian insufficiency (POI). POI, the most common cause of which is Turner's syndrome, which is the monosomy of sex chromosomes leading to a 45X karyotype, is characterized by folliculogenesis deficiency, estrogen reduction, oocyte loss and infertility (Nelson , 2009).

Although ASRM has published guidelines that it is not necessary to look at the prolactin level in the first controls; WHO accepts prolactinoma as the

leading cause of female infertility (Breitkopf and Hills, 2019). Prolactin causes low LH levels by suppressing hypothalamic GnRH secretion. In this case, anovulation; that is, it results in oligomenorrhea or amenorrhea. Prolactinoma is also considered as an etiology of luteal phase defects that cause infertility. When the prolactin level is above 100 ng/mL, overt hypogonadism and amenorrhea are seen, commonly caused by pituitary adenomas (Seppälä et al., 1976).

3.2. Endometriosis

The presence of endometrial tissue outside the uterine cavity is defined as endometriosis. 10% to 15% of women of reproductive age are affected by endometriosis, and 40% to 50% of these women will experience infertility problems(Olive and Pritts, 2001);(Prescott et al., 2016). Endometriosis is divided into four stages, from minimal to severe, according to the American Society for Reproductive Medicine (Macer and Taylor, 2012). In Stages I and II, increase in prostaglandins and cytokines, proliferation in macrophages and natural killer cells and the resulting inflammation, and this inflammation disrupting ovarian and tube functions, are thought to be associated with infertility (Bulun , 2009); (Gupta et al., 2008) . Pelvic adhesions and/or masses that disrupt the pelvic anatomy and their disruption of tubal motility, oocyte release and sperm motility are listed as Stages III and IV (Holoch and Lessey , 2010).

3.3. Pelvic/tubal adhesion

Infectious events in the abdomen are the main cause of pelvic/tubal adhesions; Pelvic inflammatory disease (PID) is the most common infectious condition affecting infertility. Chlamydia trachomatis is the most common cause of infertility with PID. The number and severity of PID attacks are effective on the possibility of being infertile (Weström et al.,1992).

Tubal abnormalities caused by acute and chronic inflammation that disrupt the structural integrity of the fallopian tubes are called hydrosalpinges. It causes tubal obstruction by preventing the distribution of physiological fluid in the fallopian tube and causing it to accumulate (Meyer et al., 1997). It has been reported in some literature that there is a 50% reduction in pregnancy if hydrosalpinx is present in infertile women who have undergone IVF treatment (Van Voorhis et al., 2019).

3.4. Uterine Causes

Space-occupying lesions in the uterus or decreased endometrial receptivity are causes of uterine infertility. A meta-analysis showed that only submucosal or intracavitary fibroids among uterine leiomyomas impair implantation and pregnancy rates (Pritts , 2001).

One study showed that the prevalence of congenital uterine abnormalities (CUA) is the same in the fertile and infertile population (Grimbizis et al., 2001).

It is thought that approximately 8% of female infertility is due to CUA. Late first trimester or second trimester CUAs have been found in 25% of women who have had period miscarriages. Uterine septum is the most commonly associated with recurrent pregnancy loss (Chan et al., 2011).

4.Current Infertility Treatment Approaches

4.1. Life-style changes

Women with abnormal body mass index (BMI) present with menstrual disorders and infertility problems. Hypogonadotropic hypogonadism is observed in women with a BMI less than 17 kg/m^2, who have eating disorders or who do intense exercise, resulting in pituitary gonadotropin secretions (Yen et al., 1973). In a study, the importance of behavior change on inducing ovulation was noted. 87% of women who resolved their energy deficiencies or behavioral problems as individually directed therapy, maintained their regular ovarian function and corrected their abnormal BMI (Berga et al. et al., 2003).

It has been observed that ovulation improves as a result of lifestyle changes and weight loss in women with a BMI greater than 27 kg/m^2 and anovulation. It has been seen in many studies that when women with obese anovulation lose 10% of their body weight; In less than 1 year, 50% to 100% of these women return to normal ovulation cycles (Crossignani et al., 2003).

Although lifestyle changes and weight loss are important for human health in many ways, in a study, the number of pregnancies and live births in obese infertile patients who received counseling for weight loss before infertility treatment and lost weight; It was observed that there was no difference between the number of pregnancies and live births in obese patients who received infertility treatment without weight loss. Accordingly, it is thought that a certain BMI is not required to start infertility treatment (Mutsaerts et al., 2016).

4.2. Ovulation induction

Clomiphene citrate (CC) is the first choice drug for induction in infertility of unknown cause. Clomiphene is a selective estrogen receptor modulator (SERM) with estrogen antagonist and agonist effects by increasing gonadotropin release from the anterior pituitary. According to the WHO classification of anovulation, while clomiphene treats class 2 anovulation, it does not have sufficient effect on WHO class 1 and class 3 anovulation.

Treatment with clomiphene is dosed for 5 consecutive days, starting from the 2nd, 3rd, 4th or 5th cycle day of the menstrual cycle, starting at 50 mg and depending on the effect on ovulation.

There is little difference in the outcome of ovulation, pregnancy or live birth compared to cycle days 2 through 5 regarding which day of the cycle treatment is started. The couple is asked to have sexual intercourse every other day for a week, starting 5 days after the last dose of the pill. It has been observed

that the probability of pregnancy may increase when clomiphene is combined with intrauterine insemination (IUI) (Wu and Winkel, 1989).

Another oral drug used for ovulation induction is letrozole. Letrozole is an aromatase inhibitor. It shows its effect by preventing the conversion of androstenedione and testosterone to estrone and estradiol and inhibiting the production of estrogen (Cole and Robinson, 1990). Like the use of clomiphene, letrozole is used for 5 days, starting with a dose of 2.5, 5 or 7.5 mg/day, depending on the effect on the 3rd, 4th, 5th, 6th, 7th cycle days of the menstrual cycle, and every other day, 5 days after the last dose sexual intercourse is requested from the couple. The FDA has approved letrozole for adjuvant treatment of breast cancer, but letrozole is used off-label for ovulation induction. Many scientific literature and committees support both the efficacy and safety of the use of letrozole in ovulation induction. ACOG agrees to use letrozole instead of clomiphene as first-line therapy for ovulation induction in women with PCOS (ACOG, 2018).

Advantages of letrozole over clomiphene:

- High rate of mono follicular development thus reducing the rate of twin pregnancies
- Shorter half-life
- No antiestrogenic effect on endometrium and central nervous system
- Low estradiol levels provide a benefit for women with breast cancer undergoing IVF

These advantages of letrozole over clomiphene indicate that it can replace clomiphene as a first-line option (Casper and Mitwally, 2006).

The more intensive treatment option for WHO Class 1, 2 or 3 anovulatory disorders is gonadotropins. They are used as a second-line treatment option for women who cannot conceive despite using clomiphene in more than one cycle. There is a study showing that the live birth rate increases with gonadotropins (Weiss et al., 2018). Depending on the treatment of infertility, multiple dose protocols can be used, but close monitoring is required when using gonadotropins. A transvaginal ultrasound check is performed every 2 to 3 days during the late follicular phase to evaluate mature dominant follicles. A desired dominant follicle should be greater than 18 mm in diameter and greater than 200 pg/mL when we control the estradiol level. In the ongoing process of treatment, after the desired dominant follicle is obtained, 250 mg subcutaneous injection of recombinant HCG or intramuscular injection of 10,000 U of urine-derived HCG is given to trigger ovulation. 24-36 hours after the injection, intrauterine insemination (IUI) is performed (Ludwig et al., 2003). IUIs can be planned in combination with all ovarian induction agents. Their clear superiority against each other has not been demonstrated and the

treatment option should be planned according to cost and patient comfort (Cantineau et al., 2010).

For patients with infertility due to bilateral tubal factors; in vitro fertilization (IVF) is the first treatment option. Women with severe tubal disease, including hydrosalpinx, should be directed to bilateral salpingectomy instead of tubal corrective surgeries, as it will cause an increase in the risk of ectopic pregnancy and worse pregnancy outcome (Johnson et al., 2010).

Although fimbrioplasty is an option for women with mild distal tubal disease, it was stated in a small study that the probability of pregnancy in mild tubal disease is equivalent to IVF, the risk of developing ectopic pregnancy is 0.7% for IVF treatment, while it is 15% in mild tubal disease (Audebert et al. et al., 2014).

Physicians should be reminded of the risk of regret in the future with all women who want tubal ligation, as a significant part of the tubal-induced infertile group consists of patients who have previously undergone bilateral salpingectomy or tubal ligation for contraception. Depending on the age of the patient, the type of ligation and the existing tubal length, the chance of pregnancy with tubal reanastomosis varies (Boeckxstaens et al., 2007).

The effect of leiomyomas on infertility and live birth rates depends on the location of the fibroids. The fibroids group that cause implantation deterioration and increase in miscarriage rates are fibroids that compress the endometrium and disrupt the uterine cavity (Pritts et al,2009). Pregnancy and live birth rates increase with the removal of these fibroids (Casini et al., 2006). In other uterine pathologies that may cause recurrent pregnancy loss and infertility, such as uterine synechiae and septa, and in the removal of fibroids, the first-line treatment is operative hysteroscopy (March and Israel, 1981). Studies have shown that asymptomatic polyps also cause infertility, and in the case of polypectomy in asymptomatic infertile women, pregnancy rates increase from 28% to 63% with IUI (Perez-Medina et al., 2005).

4.3.IVF Procedures

First, controlled ovarian hyperstimulation is achieved with injectable gonadotropins. The specialist performs transvaginal ultrasound-guided needle aspiration oocyte retrieval thirty-six hours after a trigger shot or HCG injection. Then the oocytes are transferred to a special medium and normal sperm are transferred to the medium for insemination. Intracytoplasmic sperm injection (ICSI) is the procedure in which a single sperm is placed directly into the egg cytoplasm and is applied in case of abnormal sperm. The resulting embryo is evaluated and graded and transferred on Day 3 or Day 5.

Preimplantation genetic testing (PGT) can be used as an additional IVF procedure in cases of advanced maternal age, repeated IVF failures with high-grade embryos, recurrent pregnancy losses, and unexplained infertility, as well as a known parental carrier for a genetic mutation or balanced translocation.

4.4. Complications

4.4.1. Multiple pregnancies

The risk of multiple reproduction has been a problem for assisted reproductive techniques from the beginning. In the US, 32% of ART pregnancies were multiple, compared with 3.4% of naturally conceived births (Sunderam et al., 2019). Chances of single, twin, or higher-grade pregnancies with IVF fresh embryo transfer CDC according to; were 62%, 29% and 3%, respectively (Yu et al., 2019). Oral ovarian induction agents, clomiphene and letrozole, have a lower risk of multiple pregnancy compared to gonadotropins. The chance of multiple pregnancy, including triplets, is 13% in ovulation induction using gonadotropins (Hansen et al., 2016).

4.4.2. Ectopic pregnancy

There is a two- to three-fold increase in the incidence of ectopic pregnancy among infertility patients. Its cause is related to tubal factor infertility (Li et al.,2015). The risk of ectopic pregnancy is highest after a tube surgery to correct tubal factor infertility (Audebert et al., 2014). Although the overall rate of ectopic pregnancies with IVF is roughly 1.3%, the risk of ectopic pregnancy with IVF fresh embryo transfer is higher than with frozen embryo transfer (London et al., 2015). There is no increase in ectopic pregnancies with the use of ovulation induction agents combined with IUI. However, in a study comparing induction with clomiphene, letrozole, and gonadotropins, ectopic pregnancy rates of 4%, 6%, and 8% were observed, respectively (Diamond et al., 2015).

4.4.3. Ovarian hyperstimulation syndrome (OHSS)

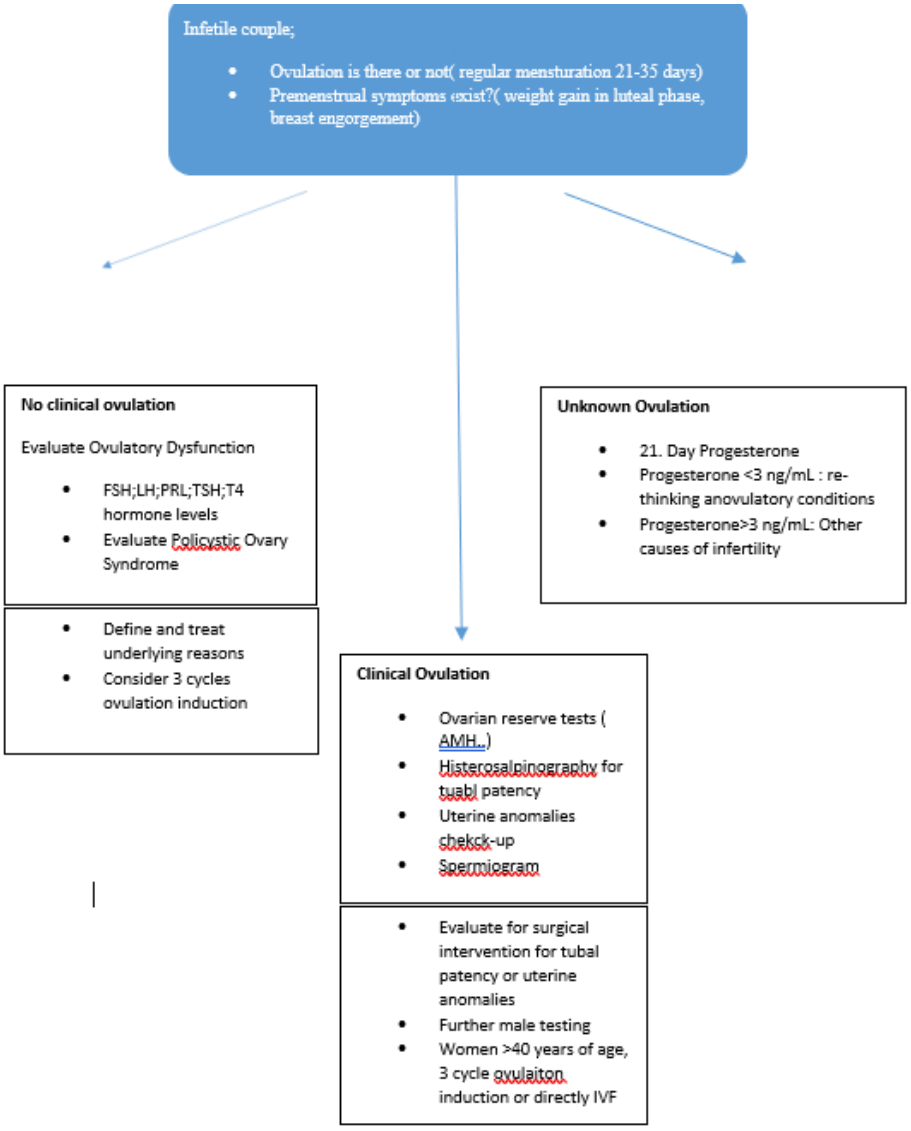
Ovarian hyperstimulation syndrome results in various signs and symptoms such as abdominal distension, nausea, vomiting, enlarged ovaries, kidney failure, venous thrombosis, acute respiratory distress syndrome, electrolyte irregularities, cardiac arrhythmias and sepsis as a result of increased capillary permeability that causes body fluids to pass through the third spaces; It is an iatrogenic complication. Severe OHSS can be fatal if left untreated (Golan et al., 1989). The risk of developing OHSS is highest in infertile patients with more than 20 mature follicles who received a trigger shot with HCG. The incidence of OHSS in IVF varies between 6% and 1% (Delvigne and Rosenberg, 2002).

Other Choices for Infertility

In specific conditions, like genetic diseases or defects in gametes in quality or quantitiy, donor oocytes or donor sperms may be considered. Donor oocyte may be indicated in medical conditions like absence of ovaries or absence of uterus. Uterus transplantation may be necessary in congenital müllerian defects.

Conclusion

Women who are not able to conceive despite 1 year of unprotected intercourse or who are older than 35 years of age and cannot achieve pregnancy despite 6 months of unprotected intercourse should be referred to specialists. General causes of infertility is represented in Table 2. As in the past, the cause and treatment of infertility is still sought through female partners, and couples should be reminded that both partners should go for checkups. The drugs and procedures used today for female infertility are well studied and well known, including their risks. Complications such as multiple pregnancy, ectopic pregnancy and OHSS risk during infertility treatment should be explained to the couples. Finally, it is a situation that should be understood by the couples that the procedures to be done before each treatment plan are well understood by the couples and the possibility of not getting pregnant even with IVF treatment. Flow chart for practical application is represented in 1. Flow chart for an infertile couple.



1. Flow Chart for an infertile couple

Table2. Causes of infertility

Ovulatory dysfunction	PCOS, Thyroid, Hypotalamic amenorrhea, Hyperprolactinemia	TSH,PRL PCOS?= 17-OHP, Total and Free Testesterone, USG, FSH/LH/E2	Thyroid and Prolactine therapies; PCOS,ovulation induction, weight loss %15; Hypogonadotropic hypogonadism, gonadotropins induction
Tubal Occlusion	Sexually transmitted infections; endometriosis; peritubal adhesions; hydrosalpinx	Hysterosalpingogram (sensitivity: 65%; specificity: 83%) Laparoscopy with chromotubation	Surgical repair (tubal reanastomosis, or fimbrioplasty for distal obstruction) or IVF
Endometirosis	Early menarche, short menstrual cycles, heavy menstrual periods, nulliparity, and family history of endometriosis	Ultrasound	Ovulation induction in mild endometirosis; surgery and then IVF in severe endometriosis
Diminished Ovarian Reserve	Age-related oocyte loss,Chemotherapy/radiation therapy	Ovarian reserve test (AMH, FSH/E2, antral follicle count)	Depends on the cause
Uterine Factors	Endometrial polyps/fibroids, uterine synechiae	TV USG, MRI, 3D ultrasound	Hysterescopic correction

REFERENCES

ACOG (2018) Committee Opinion No. 738: Aromatase Inhibitors in Gynecologic Practice. Obstetrics and Gynecology. June;131(6):1.

Aschheim, S., & Zondek, B. (1928). Schwangerschaftsdiagnose aus dem Harn (durch Hormon-Nachweis). *Klinische Wochenschrift*, *7*(1), 8-9.

Audebert, A., Pouly, J. L., Bonifacie, B., & Yazbeck, C. (2014). Laparoscopic surgery for distal tubal occlusions: lessons learned from a historical series of 434 cases. *Fertility and Sterility*, *102*(4), 1203-1208.

Barnes, J. (Ed.). (1984). *Complete works of Aristotle, volume 1: The revised Oxford translation* (Vol. 1). Princeton University Press.

Bayer, S. R., Alper, M. M., & Penzias, A. S. (2008). Boston IVF İnfertilite El Kitabı.(2. Baskı)(Çev. Işık Ahmet Zeki, Vicdan Kubilay) İstanbul: Nobel Tıp Kitabevi.

Berga, S. L., Marcus, M. D., Loucks, T. L., Hlastala, S., Ringham, R., & Krohn, M. A. (2003). Recovery of ovarian activity in women with functional hypothalamic amenorrhea who were treated with cognitive behavior therapy. *Fertility and sterility*, *80*(4), 976-981.

Breitkopf, D. M., & Hill, M. (2019). Infertility Workup for the Women's Health Specialist. *Obstetrics and Gynecology*, *133*(6), E377-E384

Boeckxstaens, A., Devroey, P., Collins, J., & Tournaye, H. (2007). Getting pregnant after tubal sterilization: surgical reversal or IVF?. *Human reproduction*, *22*(10), 2660-2664

Boivin, J., Bunting, L., Collins, J. A., & Nygren, K. G. (2007). International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. *Human reproduction*, *22*(6), 1506-1512.

Bulun SE.(2009).Endometriosis. The New England Journal of Medicine. January ;360(3):268-279

Cantineau, A. E., Janssen, M. J., Cohlen, B. J., & Allersma, T. (2014). Synchronized approach for intrauterine insemination in subfertile couples. *Cochrane Database of Systematic Reviews*, (12).

Casini, M. L., Rossi, F., Agostini, R., & Unfer, V. (2006). Effects of the position of fibroids on fertility. *Gynecological Endocrinology*, *22*(2), 106-109.

Casper, R. F., & Mitwally, M. F. (2006). Aromatase inhibitors for ovulation induction. *The Journal of Clinical Endocrinology & Metabolism*, *91*(3), 760-771.

Chan, Y. Y., Jayaprakasan, K., Zamora, J., Thornton, J. G., Raine-Fenning, N., & Coomarasamy, A. (2011). The prevalence of congenital uterine anomalies in unselected and high-risk populations: a systematic review. *Human reproduction update*, *17*(6), 761-771.

Cole, P. A., & Robinson, C. H. (1990). Mechanism and inhibition of cytochrome P-450 aromatase. *Journal of medicinal chemistry*, *33*(11), 2933-2942.

Crosignani, P. G., Colombo, M., Vegetti, W., Somigliana, E., Gessati, A., & Ragni, G. (2003). Overweight and obese anovulatory patients with polycystic ovaries: parallel improvements in anthropometric indices, ovarian physiology and fertility rate induced by diet. *Human reproduction*, *18*(9), 1928-1932.

De Graaf, R. (1965). De mulierum organis generation inservientibus, 1672: Facsimile. In *De mulierum organis generationi inservientibus, 1672*. Brill.

Delvigne, A., & Rozenberg, S. (2002). Epidemiology and prevention of ovarian hyperstimulation syndrome (OHSS): a review. *Human reproduction update*, *8*(6), 559-577.

Diamond, M. P., Legro, R. S., Coutifaris, C., Alvero, R., Robinson, R. D., Casson, P., ... & Zhang, H. (2015). Letrozole, gonadotropin, or clomiphene for unexplained infertility. *New England Journal of Medicine*, *373*(13), 1230-1240.

Eastman, N. J. (Ed.). (1991). *Soranus' gynecology*. JHU Press.

Fauser, B. C., & van Heusden, A. M. (1997). Manipulation of human ovarian function: physiological concepts and clinical consequences. *Endocrine reviews*, *18*(1), 71-106.

Golan, A., RON-EL, R. A. P. H. A. E. L., HERMAN, A., & SOFFER, Y. (1989). Ovarian hyperstimulation syndrome: an update review. *Obstetrical & gynecological survey*, *44*(6), 430-440.

Grimbizis, G. F., Camus, M., Tarlatzis, B. C., Bontis, J. N., & Devroey, P. (2001). Clinical implications of uterine malformations and hysteroscopic treatment results. *Human reproduction update*, *7*(2), 161-174.

Gupta, S., Goldberg, J. M., Aziz, N., Goldberg, E., Krajcir, N., & Agarwal, A. (2008). Pathogenic mechanisms in endometriosis-associated infertility. *Fertility and sterility*, *90*(2), 247-257.

Guttmacher, A. F. (1943). The role of artificial insemination in the treatment of human sterility. *Bulletin of the New York Academy of Medicine*, *19*(8), 573.

Hansen, K. R., He, A. L. W., Styer, A. K., Wild, R. A., Butts, S., Engmann, L., ... & Eunice Kennedy Shriver National Institute of Child Health. (2016). Predictors of pregnancy and live-birth in couples with unexplained infertility after ovarian stimulation–intrauterine insemination. *Fertility and sterility*, *105*(6), 1575-1583.

Holoch, K. J., & Lessey, B. A. (2010). Endometriosis and infertility. *Clinical obstetrics and gynecology*, *53*(2), 429-438.

Hull, M. G. R. (1987). Epidemiology of infertility and polycystic ovarian disease: endocrinological and demographic studies. *Gynecological Endocrinology*, *1*(3), 235-245.

Ivanoff, E. I. (1922). On the use of artificial insemination for zootechnical purposes in Russia. *The Journal of Agricultural Science*, *12*(3), 244-256.

Michael Ludwig, M., Doody, K. J., & Doody, K. M. (2003). Use of recombinant human chorionic gonadotropin in ovulation induction. *Fertility and sterility*, *79*(5), 1051-1059.

Johnson, N., van Voorst, S., Sowter, M. C., Strandell, A., & Mol, B. W. J. (2010). Surgical treatment for tubal disease in women due to undergo in vitro fertilization. *Cochrane Database of Systematic Reviews*, (1).

KOHLBERG K. (1953). Die Praxis der Samenübertragung beim Menschen [The practice of artificial insemination in humans]. *Deutsche medizinische Wochenschrift (1946)*, *78*(23), 835–839. https://doi.org/10.1055/s-0028-1131375

Labat, R. (1951). Traité akkadien de diagnostics et pronostics médicaux/2 Planches. *Traité akkadien de diagnostics et pronostics médicaux*.

Lefebvre, G. (1952). *Tableau des parties du corps humain mentionnées par les Egyptiens*. l'Institut français d'archéologie orientale.

Li, C., Zhao, W. H., Zhu, Q., Cao, S. J., Ping, H., Xi, X., ... & Zhang, J. (2015). Risk factors for ectopic pregnancy: a multi-center case-control study. *BMC pregnancy and childbirth*, *15*(1), 1-9.

Londra, L., Moreau, C., Strobino, D., Garcia, J., Zacur, H., & Zhao, Y. (2015). Ectopic pregnancy after in vitro fertilization: differences between fresh and frozen-thawed cycles. *Fertility and sterility*, *104*(1), 110-118.

Macer, M. L., & Taylor, H. S. (2012). Endometriosis and infertility: a review of the pathogenesis and treatment of endometriosis-associated infertility. *Obstetrics and Gynecology Clinics*, *39*(4), 535-549.

Machen, G. L., & Sandlow, J. I. (2020). Causes of male infertility. In *Male Infertility* (pp. 3-14). Springer, Cham.

March, C. M., & Israel, R. (1981). Gestational outcome following hysteroscopic lysis of adhesions. *Fertility and sterility*, *36*(4), 455-459.

Mascarenhas, M. N., & Flaxman, S. R., Boerma, T., Vanderpoel, S., & Stevens, GA (2012). *PLoS Medicine*, *9*(2), 1-12.

Meyer, W. R., Castelbaum, A. J., Somkuti, S., Sagoskin, A. W., Doyle, M., Harris, J. E., & Lessey, B. A. (1997). Hydrosalpinges adversely affect markers of endometrial receptivity. *Human reproduction (Oxford, England)*, *12*(7), 1393-1398.

Morice, P. (1992). *La gynécologie et l'obstétrique en Égypte pharaonique* (Doctoral dissertation, Éditeur inconnu).

Morice, P., Josset, P., Chapron, C., & Dubuisson, J. B. (1995). History of infertility. *Human reproduction update*, *1*(5), 497-504.

Mutsaerts, M. A., van Oers, A. M., Groen, H., Burggraaff, J. M., Kuchenbecker, W. K., Perquin, D. A., Koks, C. A., van Golde, R., Kaaijk, E. M., Schierbeek, J. M., Oosterhuis, G. J., Broekmans, F. J., Bemelmans, W. J., Lambalk, C. B., Verberg, M. F., van der Veen, F., Klijn, N. F., Mercelina, P. E., van Kasteren, Y. M., Nap, A. W., … Hoek, A. (2016). Randomized Trial of a Lifestyle Program in Obese Infertile Women. *The New England journal of medicine*, *374*(20), 1942–1953.

Nelson L. M. (2009). Clinical practice. Primary ovarian insufficiency. *The New England journal of medicine*, *360*(6), 606–614.

NOVAK, E. (1950). Genealogy of Gynaecology. *Obstetrical & Gynecological Survey*, *5*(5), 775.

Odisho AY, Nangia AK, Katz PP, Smith JF. Temporal and geospatial trends in male factor infertility with assisted reproductive technology in the United States from 1999–2010. Fertil Steril. 2014;102(2):469–475. doi:10.1016/j.fertnstert.2014.05.006

Olive, D. L., & Pritts, E. A. (2001). Treatment of endometriosis. *The New England journal of medicine*, *345*(4), 266–275.

Pérez-Medina, T., Bajo-Arenas, J., Salazar, F., Redondo, T., Sanfrutos, L., Alvarez, P., & Engels, V. (2005). Endometrial polyps and their implication in the pregnancy rates of patients undergoing intrauterine insemination: a prospective, randomized study. *Human reproduction (Oxford, England)*, *20*(6), 1632–1635.

Prescott, J., Farland, L. V., Tobias, D. K., Gaskins, A. J., Spiegelman, D., Chavarro, J. E., Rich-Edwards, J. W., Barbieri, R. L., & Missmer, S. A. (2016). A prospective cohort study of endometriosis and subsequent risk of infertility. *Human reproduction (Oxford, England)*, *31*(7), 1475–1482.

Pritts E. A. (2001). Fibroids and infertility: a systematic review of the evidence. *Obstetrical & gynecological survey*, *56*(8), 483–491.

Pritts, E. A., Parker, W. H., & Olive, D. L. (2009). Fibroids and infertility: an updated systematic review of the evidence. *Fertility and sterility*, *91*(4), 1215–1223.

RENOUARD, V. P. (1861). *Lettres sur la médecine au XIXe siècle*.

Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group (2004). Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Human reproduction (Oxford, England)*, *19*(1), 41–47

Rubin, I. C. (1920). NONOPERATIVE DETERMINATION OF PATENCY OF FALLOPIAN TUBES IN STERILITY: INTRA-UTERINE INFLATION WITH OXYGEN, AND PRODUCTION OF AN ARTIFICIAL PNEUMOPERITONEUM. *Journal of the American Medical Association*, *74*(15), 1017-1017.

Rutstein, S. O., & Shah, I. H. (2004). Infecundity, infertility, and childlessness in developing countries. Demographic and Health Surveys (DHS) Comparative reports No. 9. *ORC Macro and the World Health Organization*.

Santoro, N., Filicori, M., & Crowley, W. F., Jr (1986). Hypogonadotropic disorders in men and women: diagnosis and therapy with pulsatile gonadotropin-releasing hormone. *Endocrine reviews*, *7*(1), 11–23.

Seppälä, M., Ranta, T., & Hirvonen, E. (1976). Hyperprolactinemia and luteal insufficiency. *Lancet (London, England)*, *1*(7953), 229–230.

Sims, J. M. (1866). *Clinical notes on uterine surgery: with special reference to the management of the sterile condition*. Robert Hardwicke.

Steptoe, P. C., & Edwards, R. G. (1978). Birth after the reimplantation of a human embryo. *Lancet (London, England)*, *2*(8085), 366.

STOUGHTON R. H. (1948). Artificial human insemination. *Nature*, *162*(4124), 790.

Sunderam, S., Kissin, D. M., Zhang, Y., Folger, S. G., Boulet, S. L., Warner, L., Callaghan, W. M., & Barfield, W. D. (2019). Assisted Reproductive Technology Surveillance - United States, 2016. *Morbidity and mortality weekly report. Surveillance summaries (Washington, D.C. : 2002)*, *68*(4), 1–23.

van der Steeg JW, Steures P, Eijkemans MJC, et al. ; Collaborative Effort for Clinical Evaluation in Reproductive Medicine Study Group. Role of semen analysis in subfertile couples. Fertil Steril. 2011;95 (3):1013–1019. doi:10.1016/j.fertnstert.2010.02.024

Van Voorhis, B. J., Mejia, R. B., Schlaff, W. D., & Hurst, B. S. (2019). Is removal of hydrosalpinges prior to in vitro fertilization the standard of care?. *Fertility and sterility*, *111*(4), 652–656.

Venturella, R., Vaiarelli, A., Cimadomo, D., Pedri, S., Lico, D., Mazzilli, R., Mocciaro, R., Rienzi, L., Di Carlo, C., Ubaldi, F. M., & Zullo, F. (2019). State of the art and emerging drug therapies for female infertility. *Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology*, *35*(10), 835–841.

Weiss, N. S., Nahuis, M. J., Bordewijk, E., Oosterhuis, J. E., Smeenk, J. M., Hoek, A., Broekmans, F. J., Fleischer, K., de Bruin, J. P., Kaaijk, E. M., Laven, J. S., Hendriks, D. J., Gerards, M. H., van Rooij, I. A., Bourdrez, P., Gianotten, J.,

Koks, C., Lambalk, C. B., Hompes, P. G., van der Veen, F., … van Wely, M. (2018). Gonadotropins versus clomiphene citrate with or without intrauterine insemination in women with normogonadotropic anovulation and clomiphene failure (M-OVIN): a randomized, two-by-two factorial trial. *Lancet (London, England)*, *391*(10122), 758–765.

Westhoff, C., Murphy, P., & Heller, D. (2000). Predictors of ovarian follicle number. *Fertility and sterility*, *74*(4), 624–628.

Weström, L., Joesoef, R., Reynolds, G., Hagdu, A., & Thompson, S. E. (1992). Pelvic inflammatory disease and fertility. A cohort study of 1,844 women with laparoscopically verified disease and 657 control women with normal laparoscopic results. *Sexually transmitted diseases*, *19*(4), 185–192.

World Health Organization. (2018). The 11th revision of the International Classification of Diseases (ICD-11). *Geneva: WHO*.

Wu, C. H., & Winkel, C. A. (1989). The effect of therapy initiation day on clomiphene citrate therapy. *Fertility and sterility*, *52*(4), 564–568.

Yen, S. S., Rebar, R., Vandenberg, G., Ehara, Y., & Siler, T. (1973). Pituitary gonadotropin responsiveness to synthetic LRF in subjects with normal and abnormal hypothalamic-pituitary-gonadal axis. *Journal of reproduction and fertility. Supplement*, *20*(0), 137–161.

Yu, B., Vega, M., Zaghi, S., Fritz, R., Jindal, S., & Buyuk, E. (2018). Comparison of perinatal outcomes following frozen embryo transfer cycles using autologous versus donor oocytes in women 40 to 43 years old: analysis of SART CORS data. *Journal of assisted reproduction and genetics*, *35*(11), 2025–2029.

Zegers-Hochschild, F., Adamson, G. D., Dyer, S., Racowsky, C., de Mouzon, J., Sokol, R., Rienzi, L., Sunde, A., Schmidt, L., Cooke, I. D., Simpson, J. L., & van der Poel, S. (2017). The International Glossary on Infertility and Fertility Care, 2017. *Human reproduction (Oxford, England)*, *32*(9), 1786–1801.

CHAPTER 9

URINARY INCONTINENCE

Res. Asst. Elif KELEŞ TAYFUR[1]
Assoc. Prof. Dr. Seda KESKİN[2]
Assoc. Prof. Dr. Deha Denizhan KESKİN[3]

[1] Ordu University, Faculty of Medicine, Obstetrics and Gynecology Department, Ordu, Turkey keleselif@hotmail.com, ORCID ID 0000-0003-0456-8210
[2] Ordu University, Faculty of Medicine, Obstetrics and Gynecology Department, Ordu, Turkey adesniksek@gmail.com, ORCID ID 0000-0002-5640-4552
[3] Ordu University, Faculty of Medicine, Obstetrics and Gynecology Department, Ordu, Turkey dehadenizhankeskin@gmail.com, ORCID ID 0000-0002-6108-7619

INTRODUCTION

According to the definition of the International Continence Society (ICS), urinary incontinence (UI) is any involuntary urinary incontinence complaint. Although urinary incontinence is common, it is a problem that negatively affects a woman's health, sociability and quality of life. Approximately 25-45% of women experience this condition. Its frequency increases with age. The incidence in women is 25% in young people, 44-57% in middle age and postmenopausal period and 75% in advanced age (Carls, 2007; Kinchen et al.,2007; Boyington et al., 2007). In a review that evaluated 16 cross-sectional studies conducted in Turkey, it was emphasized that the prevalence of urinary incontinence in women in Turkey is between 16.4% and 49.7%. When the subtypes are evaluated proportionally, mixed urinary incontinence ranges between 7.8% and 64%, urge urinary incontinence ranges between 2.9% and 43% and stress urinary incontinence ranges between 20.8% and 68% (Basak et al., 2012). In a study conducted in our country, when the complaints of women suffering from urinary incontinence were evaluated, it was recorded that 42.9% of them had stress type, 27.3% had urgency type and 29.8% had mixed type urinary incontinence (Turan et al., 1996). The urethra and bladder form the lower urinary system and this anatomical formation, also called the vesicourethral unit, performs urinary filling and emptying. With the inability to perform functions, urinary retention and incontinence occur, which are signs of impaired filling and excretory function. Evaluation of the patient suffering from urinary incontinence includes anamnesis, physical examination and laboratory studies; and if clinically necessary, endoscopic and radiographic examinations are resorted to. In terms of diagnosis, urodynamic studies provide objective data to physicians (Chapple and Milsom, 2012).

1. Predisposing Factors

When urinary incontinence evaluated; age, sex, race, smoking, birth, sex hormones, menopause, medications, family history, previous pelvic surgery, pelvic organ prolapse, obesity and chronic constipation take attention as risk factors.

1.1.Age:

According to the results of studies examining the relationship of urinary incontinence types with age groups; stress-type urinary incontinence is more common in young people and women in the middle age group, and mixed-type urinary incontinence is more common in later ages (Hunskaar et al., 2003).

1.2.Sex:

Urinary incontinence is 2-3 times more common in women than in men (Ergen, 2000). This distinction is especially noticeable in people under the age

of 60. The incidence increases with age. The capacities of all body systems decrease inversely proportional to age. As age progresses in both sexes,

bladder capacity, bladder compliance and urinary flow rate decrease. In addition, considering the irrepressible bladder contractions; post-void residual urine volume increases with aging. Carlile et al. (1988) found that both the maximum urethral closure pressure and the length of the functional urethra decrease with age (Carlile et al., 1988).

1.3.Race:

In studies, the incidence of stress incontinence was found to be 61% in white women, but 27% in black women. Moreover, the incidence of urge incontinence was reported to be 56% in the black race, compared to 28% in the white race. In addition, race is a stronger predisposing factor for stress incontinence compared to other risk factors such as age, obesity, smoking and birth (Bump, 1993; Graham and Mallett, 2001).

1.4. Obesity:

An increased body mass index is a risk factor for the development of urinary incontinence. The risk is 1.3 for those with a body mass index between 25 and 30, while over 40 it is 3.29. It has been observed that weight gain damages the pelvic floor muscles and there is an improvement in urinary incontinence with weight loss (Bump et al., 1992).

1.5. Birth:

Relaxation of the pelvic floor muscles during childbirth can lead to disruption in the structures of the pelvic floor organs, damage to the pelvic nerves and damage to the external sphincter, leading to urinary incontinence (Tapp et al., 1988; Allen et al., 1990).

In addition, obstetric risk factors such as parity, type of birth, multiple pregnancies and birth of a large baby also play an important role in the development of urinary incontinence. According to the studies conducted; although there was no difference in the frequency of incontinence in women who had previously given birth to one, two or three, there was an increase in women who had given birth to four or more (Thom, 1998).

The fact that the birth weight is over 4000 grams, episiotomy, vacuum, and forceps applications increase the risk of urinary incontinence. After cesarean section, the pelvic floor muscles are still strong and urinary incontinence is less common (Deindl et al., 1994).

1.6. Urinary tract infections:

In women; urinary incontinence is frequently seen as a result of common urinary tract infections. Urinary incontinence occurs especially in the first few days after acute infection (Moore et al., 2008).

1.7. Drugs:

Some drugs (presented in Table 1); as a result of their effects on the sympathetic and parasympathetic nervous systems, cause urinary incontinence by accelerating the formation of urine. Examples include diuretics, alcohol, narcotic analgesics, anticholinergics, alpha agonists, anxiolytics/ benzodiazepines and antipsychotics. (Yalçın, 2000)

Table 1. Drugs and incontinence effects

NSAIDs	Pedal edema causing nocturnal polyuria
Sedative hypnotics	Sedation, delirium, immobility
Narcotic analgesics	Urinary retention, fecal impaction, sedation, delirium
Loop diuretics	Polyuria, frequency, urgency
GABAnergic agents (Gabapentin and pregabalin)	Edema causing nocturia and nighttime incontinence
Alcohol	Increased frequency, urgency, sedation, immobility
α-Adrenergic blockers	Stress leakage
ACE inhibitors	Cough worsens stress incontinence
Cholinesterase inhibitors	Urinary incontinence, interactions with antimuscarinics
Thiazolidinediones	Pedal edema causing nocturnal polyuria
Calcium channel blockers	Impaired detrusor contractility and retention; dihydropyridine agents can cause pedal edema, leading to nocturnal polyuria
Anticholinergics	Impaired emptying, retention, delirium, sedation, constipation, fecal impaction
Antipsychotics	Anticholinergic effects and rigidity and immobility

ACE = angiotensin-converting enzyme; GABA = γ-aminobutyric acid; NSAID = nonsteroidal anti-inflammatory drug; TCA = tricyclic antidepressant.

1.8. Sex hormones ve menopause:

Hypoestrogenemia can lead to histological changes such as epithelial atrophy, collagen loss, and devascularization in the uterus, vagina and urethra. These changes can cause urinary incontinence and recurrent urinary tract infections in a person (Robinson and Cardozo, 2003). In addition, in postmenopausal stress incontinence; while no improvement was shown after 6 months of oral estrogen therapy, it was shown that there would be improvement in symptoms after vaginal estrogen therapy (Jackson et al., 1999).

1.9. Pelvic organ prolapse:

Pelvic organ prolapse (POP) and urinary incontinence, which are gynecological problems, are often seen together; because both often originate from pelvic floor insufficiency. Hypermobility of the bladder neck and consequent stress urinary incontinence is common in women with prolapse of the anterior vaginal wall (Burrows et al., 2004).

1.10. Radiotherapy:

Due to fibrotic bladder damage, which is seen as a complication after radiotherapy as a treatment modality in invasive bladder cancer; urgency and stress urinary incontinence are observed in approximately 50% of patients (Vale et al., 1991).

2. Types

Urinary incontinence can be acute or chronic. Acute urinary incontinence, which lasts less than six months, occurs suddenly and can improve when the underlying cause is eliminated (Dowling-Castronovo and Specht, 2009).

Chronic urinary incontinence that lasts longer than six months is characterized as stress, urgency, mixed, nocturia, involuntary and other incontinence. Among these, stress urinary incontinence is the most common type (Haylen et al., 2010; Ozkan et al., 2019).

2.1. Stress urinary incontinence

It is a urinary incontinence condition that is caused by efforts such as sneezing, coughing or exercise. Stress urinary incontinence as a result of urethral sphincter insufficiency or urethral hypermobility occurs in 25% - 45% of women over the age of 30 (Khandelwal and Kistler, 2013).

2.2. Urge urinary incontinence

Urge-type urinary incontinence, which is observed due to excessive activity of the bladder detrusor muscle, causes involuntary urinary incontinence with the need to drain urine urgently, and urinary incontinence is typical in these patients while catching up with the toilet. It is observed in 9% of middle-aged women and 31% of older women. Stress urinary incontinence is the most common in women; urgency-type incontinence is the most common in older women (Khandelwal and Kistler, 2013).

Also, urinary incontinence of the urgency type can be observed in different forms. Between voluntary urination, for example, frequent but low urinary incontinence can be observed, as can high urinary incontinence.

2.3. Mix type urinary incontinence

Urge and stress-type urinary incontinence are seen together, and their prevalence is between 20% and 30%.

2.4. Enuresis noktura:

The person is incontinent after falling asleep. Urinary incontinence is only seen in the form of urgency while asleep or after falling asleep in a way that wakes the patient up from sleep.

2.5. Others:

Urinary incontinence is associated with urinary retention, Constant urinary incontinence, insensible urinary incontinence, functional urinary incontinence, coital urinary incontinence, multifactorial urinary incontinence.

3. Evalution

3.1.Anamnesis and physical examination

First of all, it is aimed at understanding the type and severity of incontinence through anamnesis. Having information about the severity of incontinence will be useful in terms of evaluation after medical or surgical treatment. For this we have to ask the patient some questions:

- *When is the beginning of the complaint?*
- *How many times a day does she miss urinating?*
- *How wet does the underwear get?*
- *How many pads does she change a day?*
- *Does urinary incontinence occur with sneezing, straining or coughing?*
- *Is there a sudden feeling of tightness and the need to go to the toilet?*
- *How many times does she urinate in a day?*
- *Is there difficulty or pain when urinating?*
- *Is she able to drain her urine completely?*
- *How much is the daily fluid intake?*
- *Does she have complaints based on the onset of postpartum?*
- *Did she undergo surgical treatment?*
- *Is there any neurological damage or disease?*
- *What are the drugs used?*

With these questions, the anamnesis should be taken in detail (Khandelwal and Kistler, 2013; Holroyd-Leduc et al., 2008; Frank and Szlanta, 2010; Wein and Rovner, 2002; Wein et al., 2012). In addition, after the anamnesis, we must resort to tests that will lead us to the diagnosis.

3.2.Coughing test:

A cough test involves observing urinary incontinence with straining or coughing, and this is a finding that supports stress-type urinary incontinence. This test should be performed while the patient is in the lithotomy position or standing and the patient's bladder should be full (Ostergard and Bent, 1985).

If the patient cannot cough enough, has just urinated, or has severe prolapse, the test may give a false negative result (Ghoniem et al., 2008; Weidner et al., 2001).

3.3. Q-tip test:

The Q-tip test is performed to assess the mobilization of the ureterovesical junction. While the patient is in the lithotomy position on the vaginal table, a sterile cotton swab is pushed 1 cm into the urethra. If an angle of more than 30 degrees occurs in the horizontal plane during straining, this condition is evaluated in favor of hypermobility and stress urinary incontinence.

3.4. Urination diary:

At the initial stage, it is recommended to keep a 3-to 7-day urination diary (Lucas et al., 2014; Yap et al., 2007). Patients are asked to write down all the details about the frequency of urinary incontinence, the number of pads used, the amount of fluid intake, how often they urinate, how much they urinate, and how often they miss urine. In addition, urination diary allows us to obtain information about how much the patient will benefit from the treatment in the future (Bryan and Chapple, 2004; Abrams and Klevmark, 1996). In stress-type urinary incontinence, a small amount of urinary incontinence is monitored in cases that will increase intra-abdominal pressure, such as coughing, straining; in urge type incontinence, urinary incontinence is monitored in varying amounts and more frequently (Khandelwal and Kistler, 2013; Moore et al., 2003; Wyman et al., 1988). In addition, if the patient urinates frequently and urinates excessively at the same time, this condition may indicate diabetes mellitus or excessive fluid intake (Culligan and Heit, 2000; Fink et al., 1999; Brown et al., 2003).

3.5. Laboratory and Imagıng

3.5.1. Complete urine analysis:

To exclude acute causes of urinary incontinence, a complete urine analysis should be performed. According to the results of the analysis, the patient should be evaluated for urinary tract infections if there is bacteriuria, possible renal failure if there is proteinuria, and diabetes mellitus if there is glucosuria (Weiss, 1998).Also, the European Association of Urology (EAU) does not recommend the treatment of asymptomatic bacteriuria in elderly patients.

3.5.2. Measurement of residual urine volume (PVR):

Current guidelines recommend PVR measurement in patients with urinary incontinence. In addition, PVR measurement contributes to assessing how much benefit patients who have started treatment due to incontinence receive from treatment (Lucas et al., 2014).

In stress, urge and mixed type urinary incontinence, the amount of postmictional residue is below 50 ML, while in overflow incontinence it is above 200 ML (Khandelwal and Kistler, 2013).

3.5.3. Urodynamics

Current guidelines do not recommend urodynamic examinations in the routine assessment of urinary incontinence. However, if surgical treatment is planned, if there is no response to medical treatment, if stress urinary incontinence can not shown with coughing or straining, if there is no healing after the incontinence surgery, if there is comorbid neurological disease, if postvoidal residu urine volume is increased, if a history of pelvic radiotherapy and if the patients have concominant pelvic organ prolapse and incontinence urodynamic investigations are recommended (Digesu et al., 2003; Radley et al., 2001; Guralnick et al., 2010).

3.5.4. Urethrocystoscopy

EAU, NICE, ICI current guidelines; while urethrocystoscopy is not routinely recommended for urinary incontinence assessment; it is recommended in patients with a history of pelvic organ prolapse and incontinence surgery, who have received pelvic radiation therapy, and suspected urethral fistula or diverticula. (European Association of Urology, National Institute for Health and Care Excellence, International Consultation on Incontinence). As a result; according to the basic guidelines, in patients presenting with urinary incontinence complaints; anamnesis, physical examination, complete urine analysis, showing stress urinary incontinence with a cough test, and measuring postvoidal urine volume are the first steps that should be applied.

4. Treatment

It is emphasized by all the guidelines that before proceeding to advanced methods of treatment in patients presenting with urinary incontinence, conservative treatments should definitely be tried. The application of conservative treatments may be more appropriate in patients who do not have advanced complaints, do not want surgery, want pregnancy, and have comorbite diseases (Siddighi and Chuan, 2006).

4.1. Conservative Treatments

4.1.1. Lifestyle Changes

Loose weight:

Weight is an important risk factor in the etiology of urinary incontinence. An increase in abdominal pressure increases intra-bladder pressure, causing urethral hypermobility, which in turn causes stress urinary incontinence and an overactive bladder with an increase in detrusor instability (American

Urological Association (AUA) Guideline, 2012; Madersbacher and Murtz, 2001).

It has been shown that with weight loss, there is a decrease in maximal intra-bladder pressure. This situation supports the notion that weight loss has an important place in the treatment of urinary incontinence (Madersbacher and Murtz, 2001; Juenemann et al., 2004). Every five-unit increase in body mass index leads to a 20-70% increase in the risk of urinary incontinence (Appell et al., 2001; Nilvebrant et al., 1997).

Quitting smoking:

Smoking, which causes chronic coughing, also causes an increase in stress-type urinary incontinence (Osca et al., 1997). Quitting smoking is recommended in the guidelines of the European Urological Association.

Regulation of the diet:

It is important to evaluate dietary habits in the history of patients admitted due to urinary incontinence complaints. Tea and caffeine-containing beverages consumed in excess should be questioned. Excessive consumption of drinks containing caffeine increases diuresis and causes urinary incontinence. There is evidence to suggest that reducing caffeine intake decreases the frequency of incontinence (Halaska et al., 2003; Zellner et al., 2009).

Considering that constipation is associated with urinary incontinence, informing the patient about avoiding foods and drinks that may cause constipation is important for the prevention of urinary incontinence (Zinner et al., 2005).

Regulation of fluid consumption:

Excess fluid consumption can aggravate urinary incontinence. Reducing fluid consumption may be recommended in patients who have excessive fluid consumption as a result of evaluating bladder logs. However, it should be remembered that reducing fluid consumption too much can also negatively affect bladder functions by causing concentrated urine and constipation (Thuroff et al., 1998).

4.1.2. Behavioral Treatments

The aim of these trainings, called behavioral treatments, is to prevent stress urinary incontinence by increasing bladder capacity or strengthening pelvic floor muscles (Shamliyan et al., 2012).

Bladder Training:

The aim of bladder training is to extend the voiding intervals of the patient with high frequency of voiding and to shorten the voiding intervals of patient with low frequency of voiding. Frequent urination causes a decrease in

bladder capacity and overactive contractions in the detrusor muscle. The patient should urinate at intervals of 3-4 hours so that regulate the frequency of urination. The effectiveness of bladder training was reported as 57% in a randomized controlled trial (Simpson and Wagstaff, 2005).

Pelvic Floor Muscle Training:

Pelvic floor muscle training is a treatment method that has been shown to be beneficial in stress, urge and mixed type urinary incontinence (Chapple et al., 2005; Lucas et al., 2014). Pelvic floor muscle exercises are recommended by NICE for at least 3 months. Studies conducted by Dr Kegel have shown that urethral sphincter function improves with the strengthening of pelvic floor muscles (Robinson and Cardozo, 2010). Pelvic floor muscle training program focuses on the levator ani, external anal sphincter and urethral sphincter. The risk of pelvic organ prolapse decreases with the strengthening of pelvic floor muscles as a result of pelvic floor muscle training (Yamaguchi et al., 2007). Pelvic floor muscle training program aims to provide a powerful and rapid contraction of the pelvic floor muscles in cases where intra-abdominal pressure increases. As a result, with increased pressure in the urethra, the urethra closes and urinary incontinence is prevented (Howard et al., 2000).

Electrical Stimulation:

Electrical stimulation can be used in the treatment of urinary incontinence. While high frequency is preferred in stress urinary incontinence, low frequency is preferred in urge type urinary incontinence. Pudental nerve stimulation is targeted by electrical stimulation and passive contraction of pelvic floor muscles and inhibition of contractions of the bladder are obtained as a result (Robert and Mainprize, 2002). In addition to mobile devices, there are also applications with vaginal, rectal or superficial electrodes (Chughtai et al., 2013). In the guidelines, while electrical stimulation is not recommended alone in stress urinary incontinence, it is recommended to apply it together with behavioral treatments in urge type incontinence (Lucas et al., 2012).

Biofeedback:

The transmission of physiological events in the body visually and audibly to the patient is called the biofeedback. Biofeedback treatment method aims to reduce the pelvic floor muscles without any contraction of the abdominal muscles. With this method, the patient learns to contract and relax the pelvic floor muscles voluntarily (Hay-Smith et al., 2011).

4.1.3.Pessaries:

The association of stress urinary incontinence and pelvic organ prolapse is frequently observed (Olsen et al., 1997). Currently, in patients with pelvic organ prolapse; vaginal pessary application is the only alternative that can be used for non-surgical treatment. Pessaries are inserted into the vagina in order to reduce pelvic organ prolapse. There are basically two types of pessaries, one

that provides support and one that fills in space. In the association of POP and SUI, pessaries that do not prevent sexual intercourse and provide support are preferred. Ring, backed ring, Gelhorn and Donut are the most preferred pessary varieties (Clemons et al., 2004). In the association of incontinence and POP, titled ring pessaries should be preferred. It is aimed to increase urethral pressure by compressing the urethra with the help of the cap. After the pessary is placed, the patient should be made to perform movements that increase intra-abdominal pressure and make sure that she is urinating without problems (Temeltas, 2013).

4.2. Medical Treatment

NICE emphasizes that medical treatment should be started with the lowest appropriate dose and that patients should also be informed that the effects of the drugs will not begin for at least 4 weeks.

4.2.1. Antimuscarinic drugs:

There are 5 subtypes of muscarinic receptors (M1-M5).M1, M2 and M3 are subtypes found in the bladder, and the most important subtype in bladder contraction is M3. Antimuscarinic agents suppress contractions of the detrusor muscle by inhibiting the postganglionic receptor domains. They affect the bladder filling phase, reduce the feeling of tightness and increase the bladder capacity (Andersson et al., 2009; Wein et al., 2012). The EUA, CUA and AUA guidelines recommend antimuscarinic agents as the first and second choice treatment for urge type urinary incontinence. Drugs in this group (fesoterodine, oxybutynin, propiverine, solifenasine, tolterodine, darifenacine, and trospiyum) compared with placebo in alleviating symptoms and healing has been found superior to placebo, although it has not been demonstrated the superiority of drugs within the same group. EAU recommends that patients who have started antimuscarinic medication should be called for a check-up within 30 days in order to control side effects. It is emphasized by the AUA that the effectiveness of the drug begins within 8-12 weeks after the start of treatment, and no dose changes should be made before it. Since muscarinic receptors are widely present in the body; there is a wide side effect profile associated with the use of antimuscarinic drugs. Headache, dry mouth, blurred vision, constipation, tachycardia, arrhythmia, itching, dyspepsia, accommodation paralysis, impaired cognitive function and drowsiness are side effects (Finney et al., 2006; Chapple et al., 2008). The EAU guideline states that antimuscarinic drugs are also effective in the elderly, but due to the side effect profile, non-drug treatments should be tried first. In the NICE guideline, it is stated that oxybutynin should not be used in the elderly, as it may adversely affect daily activities. Antimuscarinic medication should be started in patients after ophthalmological evaluation in terms of narrow-angle glaucoma.

Antimuscarinic drugs are contraindicated in the presence of arrhythmia, narrow-angle glaucoma, myasthenia gravis, gastric retention, previous

myocardial infarction, advanced liver failure or urinary retention (Davila et al., 2006).

4.2.2. Alfa-adrenergic drugs:

In patients with SUI, no superiority over placebo has been shown. (EAU).

4.2.3. Beta-adrenergic drugs:

It is recommended as a second-line treatment option in patients with urge type urinary incontinence when antimuscarinic therapy cannot be responded to. Mirabegron, a beta-adrenergic drug; due to its mild adrenergic side effects, its use in urge type urinary incontinence is recommended by the EAU guidelines.

4.2.4. Duloxetine

Although it is an option for the temporary treatment of SUI and mixed-type urinary incontinence, it is emphasized in the EAU and ICI guidelines that it should not be recommended to patients with cure expectations, given the rare but serious side effects of GIS and SSS.

4.2.5. Desmopresin

Desmopressin, a synthetic analogue of antidiuretic hormone, reduces urinary incontinence for about 4 hours in the treatment of nocturia. However, long-term use is not recommended by current guidelines, as it may lead to hyponatremia if used regularly and for a long time. It is also contraindicated in patients with renal insufficiency and heart failure due to the side effect of hyponatremia (Weatherall, 2004).

4.2.6. Estrogen

Vaginal estrogen therapy can be applied as conjugated estriol or estradiol, with vaginal pessaries, vaginal creams or rings. In the postmenopausal period, intravaginal estrogen therapy is effective in the treatment of urge type incontinence, while it is not effective in the treatment of SUI. Although the duration of treatment is not clearly indicated, postmenopausal patients should be administered intravaginally for a long time instead of systemic treatment (Lucas et al., 2014). ICI recommends that the patient be taken for further examination if urinary incontinence is associated with any of the conditions of chronic pain, pelvic organ prolapse (POP), hematuria, recurrent urinary tract infection and a history of pelvic radiation. The gold standard in advanced examination is urodynamics.

4.3. Further Treatment of Urinary Incontinence

4.3.1. Surgical Treatment

If no response is obtained after conservative and behavioral treatments are applied, surgical treatment can be switched to. Current guidelines suggest that if surgical treatment is planned any of anti-incontinence surgery(miduretral sling, burch colposuspesion, autologous fascia, pubovaginal sling, urethral filler injections) can be selected. ACOG, FIGO and EAU have accepted synthetic mid-urethral sling (MUS) as the first effective and reliable option for women who will undergo surgical treatment for stress urinary incontinence. However, if the mid urethral sling cannot be applied, they argue that the other option, LT-LS colposuspension or autologous facial slings, should be recommended.

Routine cystoscopy is recommended by the AUA to reduce the risk of complications after all mid urethral sling applications. The guidelines emphasize that if there is simultaneous stress urinary incontinence in patients undergoing pelvic organ prolapse surgery, the two should be repaired together.

Table 2. The FIGO 2017 guideline specifies the types of surgery recommended for patients with stress urinary incontinence according to specific circumstances.

Situations	First recommend	other
SUI	TOT, TVT	PVS, BC
Mixed SUI	TVT, TOT	PVS, BC
Concomittant POP	TOT, TVT, BC	PVS
İntrensek sphinkter insuffiency	TVT, PVS, TOT	BK, Urethral injection, TOT, AUS
Surgical failure	TVT, PVS, BC	TOT, Urethral injection, AUS
İmmunity disease	BC	PVS, TVT, TOT
≥65 age	TOT	TVT, Urethral injection, BC, PVS
Morbide obesity	TOT	TVT, BC, PVS

SUI: Stress urinary incontinence, TOT: Transobturator tape, TVT: Transvaginal tape
PVS: Pubovaginal sling, BC: Burch colposuspension, POP: Pelvic organ prolapse,
İSI: İntrensek sphinkter insuffiency, AUS: Artificial urethral sphincter

4.3.2. Botulinum Toxin Applications

Botulinum toxin is used for treatment in many areas with the aim of preventing unwanted muscle activities or reducing smooth muscle tone. It has been shown that botulinum toxin inhibits the bladder detrusor muscle in urge type incontinence. It results in significant improvement in symptoms (Jankovic

et al., 2009). In urge incontinence patients who do not respond to conservative and medical treatments; it is reported by EAU and ACOG that botulinum toxin (100U) injection is superior to placebo in improving their symptoms and improving their quality of life. Before the injection, the patient should be informed that the recovery continues temporarily, that there will be repeated injections, that there may be an increased risk of urinary tract infection and that there may be needs for bladder catheterization.

4.3.3. Sacral nerve modulation

In patients with urge type urinary incontinence who do not respond to conservative and or antimuscarinic treatments; EAU recommends sacral nerve neuromodulation. Studies have shown that sacral neuromodulation therapy improves symptoms and improves quality of life before invasive surgical interventions in patients who cannot respond to conservative and medical treatment (Schmidt et al., 1999).

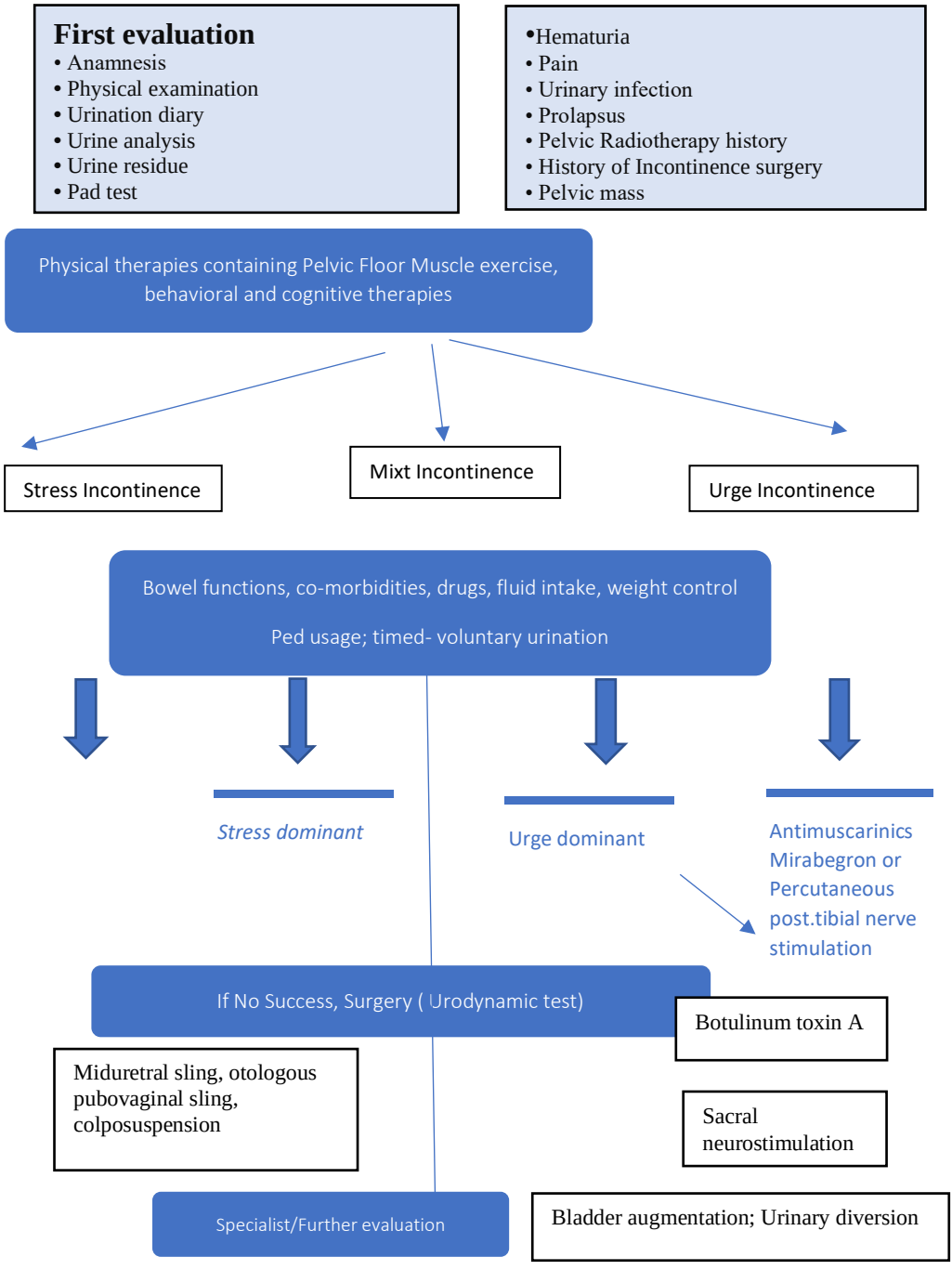
4.3.4. Bladder Neck Injection and Artificial Sphincter Applications in Women

ACOG recommends paraurethral injection in patients who cannot tolerate surgical treatment, have comorbid severity disease, do not improve after surgical treatment, or repeat complaints after showing improvement. However, the treatment provides improvement for 3 months and repeated applications are needed.

Artificial sphincter implantation is reported by EAU as a method that can be applied in experienced centers in stress urinary incontinence patients with severe sphincter insufficiency.

The flow chart (1. Incontinence flow chart) in case of urinary incontinence is shared below for practical application.

1. Incontınence flow chart



REFERENCES

Abrams, P., Klevmark, B. (1996). Frequency volume charts: an indispensable part of lower urinary tract assessment. *Scandinavian journal of urology and nephrology. Supplementum*, *179*, 47-53.

Abrams, P., Freeman, R., Anderstrom, C. (1998). Tolterodine, a new antimuscarinic agent: As effective but better tolerated than oxybutynin in patients with an overactive bladder. British Journal of Urology 81: 801-810.

Allen, R.E., Hosker, G.L., Smith, A.R.B., Warrell, D.W. (1990). Pelvic floor damage and childbirth: a neurophysiological study. *BJOG: An International Journal of Obstetrics and Gynaecology 97*(9): 770-779.

Anafarta, K., Gogus, O., Beduk, O., Arikan, N. (2000). Temel Uroloji. Gunes Kitabevi, Ankara.

Andersson, K.E., Yoshida, M. (2003). Antimuscarinics and the overactive detrusor which is the main mechanism of action?. *European urology 43* (1):1-5.

Andersson, K.E., Chapple, C.R., Cardozo, L., Cruz, F., Hashim, H., Michel, M.C., Wein, A.J. (2009). Pharmacological treatment of overactive bladder: report from the International Consultation on Incontinence. *Current opinion in urology 19* (4): 380-394.

Appell, R.A., Abrams, P., Drutz, H.P., Van Kerrebroeck, P.E.V.A., Millard, R., Wein, A. (2001). Treatment of overactive bladder: long-term tolerability and efficacy of tolterodine. *World Journal of Urology 19* (2): 141-147.

Basak, T., Uzun, S., Arslan, F. (2012). Incontinence features, risk factors, and quality of life in Turkish women presenting at the hospital for urinary incontinence. *Journal of Wound Ostomy and Continence Nursing 39* (1): 84-89.

Boyington, J.E., Howard, D.L., Carter-Edwards, L., Gooden, K.M., Erdem, N., Jallah, Y., Busby-Whitehead, J. (2007). Differences in resident characteristics and prevalence of urinary incontinence in nursing homes in the southeastern United States. *Nursing research 56* (2): 97-107.

Brown, J.S., McNaughton, K.S., Wyman, J.F., Burgio, K.L., Harkaway, R., Bergner, D., Girman, C.J. (2003). Measurement characteristics of a voiding diary for use by men and women with overactive bladder. *Urology 61* (4): 802-809.

Bryan, N.P., Chapple, C.R. (2004). Frequency volume charts in the assessment and evaluation of treatment: how should we use them? *European urology 46* (5): 636-640.

Bump, R.C., Sugerman, H.J., Fantl, J.A., McClish, D.K. (1992). Obesity and lower urinary tract function in women: effect of surgically induced weight loss. *American journal of obstetrics and gynecology 167* (2): 392-399.

Bump, R.C. (1993). Racial comparisons and contrasts in urinary incontinence and pelvic organ prolapse. *Obstetrics and gynecology 81* (3): 421-425.

Burrows, L.J., Meyn, L.A., Walters, M.D., Weber, A.M. (2004). Pelvic symptoms in women with pelvic organ prolapse. *Obstetrics and Gynecology 104* (5 Part 1): 982-988.

Carlile, A., Davies, I., Rigby, A., Brocklehurst, J.C. (1988). Age changes in the human female urethra: a morphometric study. *The Journal of urology 139* (3): 532-535.

Carls, C. (2007). The prevalence of stress urinary incontinence in high school and college-age female athletes in the midwest: implications for education and prevention. *Urologic Nursing 27* (1): 21-4.

Chapple, C.R., Martinez-Garcia, R., Selvaggi, L., Toozs-Hobson, P., Warnack, W., Drogendijk, T., Star Study Group. (2005). A comparison of the efficacy and tolerability of solifenacin succinate and extended release tolterodine at treating overactive bladder syndrome: results of the Star trial. *European urology 48* (3): 464-470.

Chapple, C.R., Khullar, V., Gabriel, Z., Muston, D., Bitoun, C. E., Weinstein, D. (2008). The effects of antimuscarinic treatments in overactive bladder: an update of a systematic review and meta-analysis. *European urology 54* (3): 543-562.

Chapple, C.R., Milsom, I. (2012). Urinary incontinence and pelvic prolapse: epidemiology and pathophysiology. Campbell-Walsh Urology 10th ed. Elsevier-Sounders, Philadelphia.

Chughtai, B., Lee, R., Sandhu, J., Te, A., Kaplan, S. (2013). Conservative treatment for postprostatectomy incontinence. *Reviews in urology 15* (2): 61.

Clemons, J.L., Aguilar, V.C., Tillinghast, T.A., Jackson, N.D., Myers, D.L. (2004). Risk factors associated with an unsuccessful pessary fitting trial in women with pelvic organ prolapse. *American journal of obstetrics and gynecology 190* (2): 345-350.

Culligan, P.J., Heit, M. (2000). Urinary incontinence in women: evaluation and management. *American Family Physician 62* (11): 2433-2444.

Davila, G.W., Ghoniem, G.M., Wexner, S.D. (2006). Pelvic Floor Dysfunction: A Multidisciplinary Approach. Springer-Verlag, London.

Deindl, F.M., Vodusek, D.B., Hesse, U., Schüssler, B. (1994). Pelvic floor activity patterns: comparison of nulliparous continent and parous urinary stress incontinent women. A kinesiological EMG study. *British Journal of Urology 73* (4): 413-417.

Digesu, G.A., Khullar, V., Cardozo, L., Salvatore, S. (2003). Overactive bladder symptoms: do we need urodynamics? *Neurourology and urodynamics 22* (2): 105-108.

Dowling-Castronovo, A., Specht, J.K. (2009). How to try this: Assessment of transient urinary incontinence in older adults. *The American Journal of Nursing 109* (2): 62-71.

Ergen, A. (2010). Asiri Aktif Mesane Degerlendirme ve Tedavi., Gunes Tip Kitabevleri, Ankara.

Fink, D., Perucchini, D., Schaer, G., Haller, U. (1999). The role of the frequency-volume chart in the differential diagnostic of female urinary incontinence. *Acta obstetricia et gynecologica Scandinavica 78* (3): 254-257.

Finney, S.M., Anderson, K.E., Gillespie, J.I., Stewart, L.H. (2006). Antimuscarinic drugs in detrusor overactivity and the overactive bladder syndrome: motor or sensory actions? *British Journal of Urology İnternational 98* (3): 503-507.

Frank, C., Szlanta, A. (2010). Office management of urinary incontinence among older patients. *Canadian Family Physician 56* (11): 1115-1120.

Ghoniem, G., Stanford, E., Kenton, K., Achtari, C., Goldberg, R., Mascarenhas, T., Petri, E. (2008). Evaluation and outcome measures in the treatment of female urinary stress incontinence: International Urogynecological Association (IUGA)

guidelines for research and clinical practice. *International Urogynecology Journal 19* (1): 5-33.

Graham, C.A., Mallett, V.T. (2001). Race as a predictor of urinary incontinence and pelvic organ prolapse. *American journal of obstetrics and gynecology 185* (1): 116-120.

Guralnick, M.L., Grimsby, G., Liss, M., Szabo, A., O'Connor, R.C. (2010). Objective differences between overactive bladder patients with and without urodynamically proven detrusor overactivity. *International urogynecology journal 21* (3): 325-329.

Halaska, M., Ralph, G., Wiedemann, A., Primus, G., Ballering-Brühl, B., Höfner, K., Jonas, U. (2003). Controlled, double-blind, multicentre clinical trial to investigate long-term tolerability and efficacy of trospium chloride in patients with detrusor instability. *World journal of urology 20* (6): 392-399.

Haylen, B.T., De Ridder, D., Freeman, R.M., Swift, S.E., Berghmans, B., Lee, J., Schaer, G.N. (2010). An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. *Neurourology and Urodynamics: Official Journal of the International Continence Society 29* (1): 4-20.

Hay-Smith, E.J.C., Herderschee, R., Dumoulin, C., Herbison, G.P. (2011). Comparisons of approaches to pelvic floor muscle training for urinary incontinence in women. *Cochrane Database of Systematic Reviews* (12).

Holroyd-Leduc, J.M., Tannenbaum, C., Thorpe, K.E., Straus, S.E. (2008). What type of urinary incontinence does this woman have? *Jama 299* (12): 1446-1456.

Howard, D., Miller, J.M., Delancey, J.O., Ashton-Miller, J.A. (2000). Differential effects of cough, valsalva, and continence status on vesical neck movement. *Obstetrics and Gynecology 95* (4): 535-540.

Hunskaar, S., Burgio, K., Diokno, A., Herzog, A.R., Hjälmås, K., Lapitan, M.C. (2003). Epidemiology and natural history of urinary incontinence in women. *Urology 62* (4): 16-23.

Jackson, S., Shepherd, A., Brookes, S., Abrams, P. (1999). The effect of oestrogen supplementation on post-menopausal urinary stress incontinence: a double-blind placebo-controlled trial. *British Journal of Urology: An International Journal of Obstetrics and Gynaecology 106* (7): 711-718.

Jankovic, J., Albanase, A., Atassi, M.Z. (2009). Botulinum toxin: Therapeutic cliinical practice and science. Saunders Elsevier, Philadelphia.

Juenemann, K., Hessdoerfer, E., Unamba-Oparah, I., Berse, M., Bruenjes, R., Madersbacher, H., Gramatte, T. (2004). Propiverine hydrochloride immediate (IR) and extended release (ER): comparison of efficacy and tolerability in patients with overactive bladder. *Neurourology And Urodynamıcs* 23 (5-6): 599-600).

Kinchen, K.S., Lee, J., Fireman, B., Hunkeler, E., Nehemiah, J.L., Curtice, T.G. (2007). The prevalence, burden, and treatment of urinary incontinence among women in a managed care plan. *Journal of Women's Health 16* (3): 415-422.

Khandelwal, C., Kistler, C. (2013). Diagnosis of urinary incontinence. American Family Physician 87(8),543-550, http://www. aafp.org/afp/2013/0415/p543.html, (Accessed July 16.07.2019).

Lightner, D.J., Gomelsky, A., Souter, L., Vasavada, S.P. (2019). Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline amendment 2019. *The Journal of urology 202* (3): 558-563.

Lucas, M.G., Bosch, R.J., Burkhard, F.C., Cruz, F., Madden, T.B., Nambiar, A. K., Pickard, R.S. (2012). EAU guidelines on assessment and nonsurgical management of urinary incontinence. *European urology 62* (6): 1130-1142.

Lucas, M.G., Bedretdinova, D., Bosch, J.L.H.R., Burkhard, F., Cruz, F., Nambiar, A.K., Pickard, R.S. (2014). EAU guidelines on urinary incontinence. *European Association of Urology. Available via http://www. uroweb. Org/gls/pdf/20% 20Urinary% 20Incontinence_LR. Pdf. Accessed, 4*.

Madersbacher, H., Mürtz, G. (2001). Efficacy, tolerability and safety profile of propiverine in the treatment of the overactive bladder (non-neurogenic and neurogenic). *World journal of urology 19* (5): 324-335.

McKertich, K. (2008). Urinary incontinence: assessment in women: stress, urge or both?. *Australian family physician 37* (3).

Moore, K.N., Saltmarche, B., Query, A. (2003). Urinary incontinence. Non-surgical management by family physicians. *Canadian Family Physician 49* (5): 602-610.

Moore, E.E., Jackson, S.L., Boyko, E.J., Scholes, D., Fihn, S.D. (2008). Urinary incontinence and urinary tract infection: temporal relationships in postmenopausal women. *Obstetrics and Gynecology 111* (2): 317-323.

Nilvebrant, L., Hallen, B., Larsson, G. (1997). Tolterodine-a new bladder selective muscarinic receptor antagonist: preclinical pharmacological and clinical data. *Life sciences 60* (13-14): 1129-1136.

Olsen, A.L., Smith, V.J., Bergstrom, J.O., Colling, J.C., Clark, A.L. (1997). Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. *Obstetrics and Gynecology* 89:501-506.

Osca, J.M., Martinez-Agullo, E., Broseta, E., Jimenez-Cruz, J.F. (1997). Trospium chloride versus oxybutynin in the treatment of bladder neurological disorders: a double blind randomized clinical trial. *British Journal of Urology 80* (2): 12.

Ostergard, D.R., Bent, A.E. (1985). Urogynecology and Urodynamics – Theory and Practice, 3rd Edition. Wi1liams and Wilkins, Philadelphia.

Ozkan, S.A., Bilgic, D., Beji, N.K. (2019). Turkiye'de hemsirelik alanında uriner inkontinansla ilgili yapılan lisansustu tezlerin incelenmesi. *ACU Sağlık Bilimleri Dergisi* 10 (2): 201-210.

PL, D., Lee, E.T.C., Hay, D.M. (1988). Obesity and urinary incontinence in woman. *British Obstetric and Gynecology 95*: 91-96.

Radley, S.C., Rosario, D.J., Chapple, C.R., Farkas, A.G. (2001). Conventional and ambulatory urodynamic findings in women with symptoms suggestive of bladder overactivity. *The Journal of urology 166* (6): 2253-2258.

Robert, M., Mainprize, T.C. (2002). In Female Pelvic Medicine and Reconstructive Pelvic Surgery. Springer, London.

Robinson, D., Cardozo, L.D. (2003). The role of estrogens in female lower urinary tract dysfunction. *Urology 62* (4): 45-51.

Robinson, D., Cardozo, L. (2010). New drug treatments for urinary incontinence. *Maturitas 65* (4): 340-347.

Schmidt, R.A., Jonas, U.D.O., Oleson, K.A., Janknegt, R.A., Hassouna, M.M., Sıegel, S.W., Van Kerrebroeck, P.E. (1999). Sacral nerve stimulation for treatment of refractory urinary urge incontinence. *The Journal of urology 162* (2): 352-357.

Shamliyan, T., Wyman, J.F., Ramakrishnan, R. (2012).Benefits and harms of pharmacologic treatment for urinary incontinence in women: A systematic review. *Annals of International Medicine* 156: 861-874.

Siddighi, S., Chuan, S. (2006). Urogynecology and Female Pelvic Reconstructive Surgery: Just the Facts. McGraw-Hill-Medical Publishing Division, New York.

Simpson, D., Wagstaff, A.J. (2005). Solifenacin in overactive bladder syndrome. *Drugs and aging 22* (12): 1061-1069.

Tapp, A., Cardozo, L., Versı, E., Montgomery, J., Studd, J. (1988). The effect of vaginal delivery on the urethral sphincter. *BJOG: An International Journal of Obstetrics and Gynaecology 95* (2): 142-146.

Temeltas, G. (2013). Stres tipi idrar kacirrma ve pelvik organ prolapsusunda cerrahi disi tedavi secenekleri. *Kadin ve İslevsel Uroloji Bulteni 3*: 5-9.

Thom, D. (1998). Variation in estimates of urinary incontinence prevalence in the community: effects of differences in definition, population characteristics, and study type. *Journal of the American Geriatrics Society 46* (4): 473-480.

Thuroff, J.W., Chartier-Kastler, E., Corcus, J., Humke, J., Jonas, U., Palmtag, H., Tanagho, E.A. (1998). Medical treatment and medical side effects in urinary incontinence in the elderly. *World journal of urology 16*: 48-61.

Turan, C., Zorlu, G., Ekin, M., Hancerlioğullari, N., Saraçoğlu, F. (1996). Urinary incontinence in women of reproductive age. *Gynecologic and obstetric investigation 41* (2): 132-134.

Vale, J.A., Trott, K.R., Withfield, H.H. (1991). Post-radiotherapy bladder dysfunction-a denervation disorder. *Neurology and Urodynamics 10* (4): 349-350.

Weatherall, M. (2004). The risk of hyponatremia in older adults using desmopressin for nocturia: a systematic review and meta-analysis. *Neurourology and Urodynamics: Official Journal of the International Continence Society 23* (4): 302-305.

Weidner, A.C., Myers, E.R., Visco, A.G., Cundiff, G.W., & Bump, R.C. (2001). Which women with stress incontinence require urodynamic evaluation? *American journal of obstetrics and gynecology 184* (2): 20-27.

Wein, A.J., Rovner, E.S. (2002). Definition and epidemiology of overactive bladder. *Urology, 60* (5): 7-12.

Wein, A.J., Kavoussi, L.R., Novick, A.C. (2012). Campbell-Walsh Urology 10th Edition. Elsevier Saunders, Philadelphia.

Wein, A.J., Kavoussi, L.R., Novick, A.C., Partin, A.W., Peters, C.A. (2012). Campbell-Walsh Urology 10th Edition. Elsevier Saunders, Philadelphia.

Weiss, B.D. (1998). Diagnostic evaluation of urinary incontinence in geriatric patients. *American family physician 57* (11): 2675.

Wyman, J.F., Choi, S.C., Harkins, S.W., Wilson, M.S., Fantl, J.A. (1988). The urinary diary in evaluation of incontinent women: a test-retest analysis. *Obstetrics and Gynecology 71* (6 Pt 1): 812-817.

Yalçın, Ö. (2000). Urojinekoloji 1st ed. Atlas Yayıncılık, Ankara.

Yamaguchi, O., Marui, E., Kakizaki, H., Itoh, N., Yokota, T., Okada, H., Japanese Solifenacin Study Group. (2007). Randomized, double-blind, placebo-and propiverine-controlled trial of the once-daily antimuscarinic agent solifenacin in Japanese patients with overactive bladder. *British Journal of Urology international 100* (3): 579-587.

Yap, T.L., Cromwell, D.C., Emberton, M. (2007). A systematic review of the reliability of frequency-volume charts in urological research and its implications for the optimum chart duration. *British Journal of Urology international 99* (1).

Zellner, M., Madersbacher, H., Palmtag, H., Stöhrer, M., Bödeker, R.H., P195 Study Group. (2009). Trospium chloride and oxybutynin hydrochloride in a german study of adults with urinary urge incontinence: results of a 12-week, multicenter, randomized, double-blind, parallel-group, flexible-dose noninferiority trial. *Clinical therapeutics 31* (11): 2519-2539.

Zinner, N., Tuttle, J., Marks, L. (2005). Efficacy and tolerability of darifenacin, a muscarinic M3 selective receptor antagonist (M3 SRA), compared with oxybutynin in the treatment of patients with overactive bladder. *World journal of urology 23* (4): 248-252.

CHAPTER 10

HUMAN PAPILLOMA VIRUS, CERVICAL CANCER and HPV VACCINES

Obstetrician and Gynecologist, M.D. Kaan Turan KARAKAYA[1]
Assoc. Prof. Dr. Seda KESKİN[2]
Assoc. Prof. Dr. Deha Denizhan KESKİN[3]

[1] Ordu University, Faculty of Medicine, Obstetrics and Gynecology Department, Ordu, Turkey turankaankarakaya@hotmail.com, ORCID ID 0000-0001-7730-7690
[2] Ordu University, Faculty of Medicine, Obstetrics and Gynecology Department, Ordu, Turkey adesniksek@gmail.com, ORCID ID 0000-0002-5640-4552
[3] Ordu University, Faculty of Medicine, Obstetrics and Gynecology Department, Ordu, Turkey dehadenizhankeskin@gmail.com, ORCID ID 0000-0002-6108-7619

INTRODUCTION

In recent years, the frequency of cervical cancer has started to decrease with the introduction of screening programs, especially in developed countries. In developing or undeveloped countries, it continues to be a health problem that threatens society. Cervical cancer ranks fourth in the ranking of cancer incidence in women. Cervical cancer requires long-term exposure to HPV infection to develop, this long-term exposure can be caught and treated at an early stage with screening programs, and cervical cancer is actually considered a preventable cancer. The majority of women with cervical cancer occur in women who have almost never been screened (Sung et al. 2000).

1.Human Papillomavirus

HPV-related cancers continue to be important for both women and men. In a number of cases, HPV was detected in almost all patients with cervical cancer (Walboomers et al. 2004).

HPV; is a circular double-stranded envelopeless DNA virus containing a protein capsid. HPV viruses are numbered by genotype and the order in which they were discovered (Zur Hausen 2002). Viruses have cutaneous or mucosal tropism according to their group. HPV also plays a role in the etiology of penile, anal, vulvar, head and neck cancers (Serrano et al. 2018).

HPV first infects basal epithelial cells as a result of microtraumas to the epithelium. HPV binds to the heparan sulfate receptors of the basal cell. The life cycle of the virus is parallel to epithelial differentiation. HPV viruses begin to multiply from the most basal cells and are completed in the cells at the surface. Since HPV is not a lytic virus, HPV virions are released when the epithelium completes its cell cycle and desquamation (Griffith et al. 2016).

To date, more than 150 HPV types have been identified. Some types of HPV are usually excreted from the body by the immune system in humans and do not cause any lesions. On the other hand, high-risk HPV types are one of the leading causes of all cervical cancer cases and other HPV-related cancers (Doorbar et al., 2012). High-risk HPV types:16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59.

HPV is usually transmitted sexually. Genital HPV infection is the most common transmitted sexually transmitted disease among women. In anogenital HPV infections, it is mainly transmitted through skin-to-skin or mucosa-to-

mucosa contact. HPV transmission occurs through epithelial injuries that occur during sexual intercourse. Transmission also includes fingers, fomite, mouth, direct skin contact. Vertical transmision of HPV from mother to baby is also observed via vaginal birth (Petca et.al.2020). Transmission of HPV via water is not proven. The most important risk factors for HPV transmission are the number of partners and the age of association (Burchell et al. 2006).

1.1.SQUAMOCOLUMNAR JUNCTION

The cervix is lower segment of uterus rich in connective tissue that connects the uterine cavity to the vagina. The lower half of the cervix mucosa adjacent to the vagina is covered with squamous epithelium, while the upper half adjacent to the uterus is covered with columnar epithelium. The place where these two different epitheliums meet is called the squamous columnar junction(SCJ) (Prendiville et al. 2017).

The location of SCJ varies with age and hormonal status. The SCJ is monitored close to the external os before the pubertal period. In the adolescent period, during the first pregnancy and due to the use of combined oral contraceptives, the SCJ turns outward on the ectocervix. Lactation is drawn into the endocervical canal only in low-estrogenic situations, such as the use of progestin-containing pills. The acidic environment in the vagina results in metaplasia of the columnar epithelium, which is more immature, into the squamous epithelium. Squamous metaplasia is a natural process; a progressive metaplastic and mature squamous epithelial band is formed starting from the original SCJ, this area is called the transformation zone (TZ). TZ is highly sensitive to HPV. Almost all cervical cancers consist of TZ. In the case of detection of a preinvasive lesion, performing an excision containing TZ provides a high chance of treatment (Prendiville et al. 2017).

1.2. Cervical Intraepithelial Neoplasia

A recurrent high-risk HPV infection is usually necessary for cervical cancer to occur. However, cervical cancer is a rare consequence of these infections. It takes about 12-15 years for high-risk HPV infection to lead to cervical cancer. Cervical intraepithelial lesions can vary in three directions. It may regress, stay the same, or cause cervical cancer. Although regression is observed more frequently in low-grade lesions, the probability of regression

decreases with increasing age. Although progression to cancer is very rare in low-grade lesions, the rate of cancer development is 5% in CIN2 and 12% in CIN3 (Massad, 2018).

Although it takes more than 10 years for high-grade lesions to progress to cervical cancer, surgical intervention is necessary because we cannot know the duration of the lesion at the time of diagnosis. With surgical intervention, the likelihood of developing cervical cancer decreases dramatically (Vink et al.2013).

1.3. Risk Factors

There is such a strong association between cervical cancer and HPV that it is difficult to assess the effects of other risk factors. Although HPV is more common in younger women, regression rates are lower in older women. Due to the weakening of the immune system due to aging, most high-risk HPV infections are accompanied by a high degree of CIN or cervical cancer. There is a positive correlation between multiple pregnancy and cervical cancer. The higher parity can keep the conversion zone active for a long time. Hormonal changes caused by pregnancy may affect the immune response to HPV (Sethi et al. 1998). Long-term use of combined oral contraceptives increases the risk of cervical cancer. The main reason for this effect of combined oral contraceptives is thought to be the increased persistence of HPV and the activation of oncogenic genes (Appleby et al., 2007). Cervical cancer is most common in women with low socioeconomic status. Women with low socioeconomic status; factors such as early sexual intercourse and difficulties in accessing screening testing are recognized to increase risk (Sanjose et al. 1997). Risk factors are represented in Table 1.

Table 1. Risk Factors of Cervical Cancer

• Early first sexual intercourse
• Smoking
• Multipartner
• Prolonged oral contraceptive use
• Multiparity
• Co-infections
• Cervical dysplasia

1.4.Cervical Cancer Screening

Cancer screening programs are carried out to identify patients who do not have any symptoms. The long duration of the preinvasive stage of cervical cancer, the availability of highly reliable screening tests and the successful treatment of early stage lesions make screening important (Saslow et al. 2012). Cervical cancer screening programs include PAP and HPV tests. The sensitivity of a single pap test is low. It can be negative in most cases of high-grade CIN. Due to the long progression of HPV infection towards cancer, the chance of multiple screening increases sensitivity. Combined use of Pap test and HPV test increased sensitivity, especially in high-grade CIN cases (Mayrand et al. 2006).

The lower age limit for starting cervical cancer screening is set at 21 by the guidelines. This limit is independent of when sexual activity begins. Early stage CIN lesions in adolescents will greatly regress without the need for treatment. Therefore, screening under the age of 21 can cause additional treatment to women of reproductive age and may do more harm than good to reproductive health.

For women aged 21-29 years, screening with a PAP test is recommended every 3 years. Screening with an HPV test is not recommended before the age of 30. While screening women younger than 30 years of age with HPV testing does not reduce the incidence of cervical cancer, it increases the risk of unnecessary colposcopy by detecting transient HPV infections (Saslow et al. 2012).

HPV and PAP tests for women aged 30-65 years are recommended to be done together every 5 years (Curry et al. 2018). Despite the longer screening interval, women who are tested together at 5-year intervals have a lower risk of developing cervical cancer compared to women who are tested for PAP at 3-year intervals (Dillner et al. 2008).

In women over the age of 65, screening is terminated if there have been two negative spousal test results in the last 10 years and more than 5 years have passed since the last negative result. After the scan is terminated, there is no need to start scanning for any reason. Women with high-grade CIN lesions; even if the lesion regresses or is treated, it should be followed for 20 years. In such patients, it is not appropriate to take the age of 65 as the upper limit in women who have undergone hysterectomy surgery. There are two situations in

which to decide on the continuation of the scan. These are incomplete removal of the cervix or the presence of a high-grade CIN lesion.

1.5. Colposcopy

Colposcopy is a method based on knowledge and experience**.** It was first implemented by Hans Hinselman in 1925. It is applied to the cervix in the form of looking directly at it in the presence of strong light sources in combination with optics that magnify the image. Biopsy is taken from suspicious regions.

Indications; suspicion of invasive cancer at the smear, HSIL (High Grade Squamous Intraepitelial Lesion) , the presence of glandular lesions, intermenstrual bleeding and postcoital hemorrhage, previous history of genital cancer, presence of HPV 16 and HPV 18 in screening.

2. Cervix Cancer

Cervical cancer is the most common cancer in women after breast cancer, and the third most common type of cancer after breast and colorectal cancer regardless of gender. Approximately 250 000 women die every year due to cervical cancer worldwide (Seigel et al 2012). Cervical cancer typically begins as a cervical intraepithelial lesion from the transformation zone of the cervix and develops into invasive cancer within a certain period of time. Cervical cancer progression rates are; 2-6% for mild dysplasia, progression in severe dysplasia is within 2-5 years with the rate of 10%. This suggests that screening tests will reduce the risk of developing invasive cancer in the years to come. (Castle et al. 2011).

2.1. Spread

With direct spread of cervical cancer, it can spread to the endocervix, lower uterine segment, parametrium, and vagina. Lymphatic route can spread to parametrial, obturatory, internal and external iliac lymph nodes. Its spread through the blood is to the lungs, mediastinum, bone and liver (Randall et al.2013).

2.2. Clinic

The most common symptom of cervical cancer is abnormal vaginal bleeding, postcoital bleeding and discharge. However, it does not show symptoms in many patients and occurs randomly during clinical examination

and cytological screening. As the tumor grows, pelvic pain can cause difficulty in urination and defecation. During the physical examination, lesions containing fragile, hemorrhagic and necrotic areas can be seen. The spread to adjacent tissues can be understood by vaginal and rectal examination. (Nasiell et al. 1986). Staging of cervical cancer is shown in Table 2.

Table 2. Cervical Cancer Staging

Stage 1	Cervical carcinoma confined to cervix
1A	Invasive carcinoma diagnosed only by microscopy
1A1	Measured stromal invasion <3 mm or less in depth.
1A2	Measured stromal invasion more than ≥3 mm and <5 mm in depth
1B	Invasive carcinoma deepest invasion ≥5 mm, limited to cervix
1B1	Invasive carcinoma deepest invasion ≥5 mm,<2cm in greatest dimension
1B2	Invasive carcinoma ≥2 cm and <4cm in greatest dimension
1B3	Invasive carcinoma ≥4cm in greatest dimension
Stage 2	Carcinoma invades beyond the uterus; but no extension to lower third of vagina or pelvic wall
2A	Invasion to the upper two-thirds of vagina wtihout parametrial involvement
2A1	Invasive carcinoma <4cm in greatest dimension
2A2	Invasive carcinoma ≥4cm in greatest dimension
2B	With parametrial involvement but not up to the pelvic wall
Stage 3	Tumor extends to pelvic wall and/or involves lower third of vagina, and/or causes hydronephrosis or nonfunctioning kidney, and/or involves pelvic and/or para-aortic lymph nodes
3A	Tumor involves lower third of vagina, no extension to pelvic wall
3B	Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctioning kidney
3C	Tumor involves pelvic and/or para-aortic lymph nodes, irrespective of tumor size and extent
3C1	Pelvic lymph node metastasis only
3C2	Para-aortic lymph node metastasis
Stage 4	Tumor invades mucosa of bladder or rectum (biopsy proven), and/or extends beyond true pelvis
4A	Tumor has spread to adjacent pelvic organs
4B	Tumor has spread to distant organ

2018 International Federation of Gynecology and Obstetrics (FIGO) Staging of Cervical Cancer (Hill E.K. 2020)

2.3. Treatment

Radiotherapy is used at all stages of the disease, while surgical treatment is used only in the initial stages of the disease**.** The use of surgery instead of radiotherapy is more advantageous in young women, for whom it is important to protect the ovaries. If radiotherapy is required, moving the ovaries surgically outside the planned radiotherapy site may provide some protection of ovarian functions in patients willing bearing child. (Landoni et al.2007).

Cervical cone biopsy (also conization) plays an important role in both diagnosis and treatment of cervical cancer. This procedure is indicated for the treatment of early-stage disease that wants to confirm the diagnosis and preserve fertility (Hopkins et al. 2000).

Hysterectomy can be performed in patients who do not want fertility. With the stage of the disease, the size of the hysterectomy may change and lymph node dissection may be added.

Radical tracheletomy is a procedure that is gaining popularity as a surgical management option for women with a desire for uterine preservation or fertility. Patients who are suitable for this procedure are those who have a tumor smaller than 2 cm and a negative lymph node (Shepherd et al. 2006). The procedure is accompanied by pelvic lymphadenectomy and the placement of cervical cerclage for further pregnancy.

3. HPV VACCINES

German virologist Zur Hausen discovered in 1983 that most of the 24 cervical cancer precursors had HPV 16 and HPV 18. Hector Frazer, on the other hand, took the most important step in vaccine production with the in vitro synthesis of virus-like particles (L1) in 1991(Zhou et al 1991). The first quadrivalent HPV vaccine was approved in 2006. In the following years, bivalent and nanovalent vaccines were approved by the FDA, respectively (Nicol et al 2016).

There are more than 170 HPVs, of which at least 13 cause cancer. HPV 16 and 18 cause 70% of cancers (de Villiers 2013). Since 2014, HPV screening has been carried out in women over the age of 30 in Turkey. In the study, the most common high-risk HPV types in Turkey were, respectively; 16,51,31,52,39,18 and 58 (Gultekin et al 2018). When the regions are examined separately, changes can be seen in the ranking. As a result of a study conducted

in 2018, it was shown that HPV 31 was detected more than HPV 51 in Ordu (Keskin, 2018). For this reason, it should be kept in mind that there may be changes in regional HPV types in screening programs.

The World Health Organization recommends routine administration of the HPV vaccine. Although there are countries where HPV vaccine is routinely administered, unfortunately our country is not among these countries. The vast majority of patients with cervical cancer in developing countries do not receive medical treatment. Therefore, the vaccine is more economically advantageous by preventing cancer. ESGO (*European Society of Gynaecological Oncology*) believes that developing countries will benefit more economically from the vaccine (Vergote et al 2017).

The quadrivalent vaccine contains HPV 6,11,16,18 types. The nanovalent vaccine contains HPV 6,11,16,18,31,33,45,52 and 58. The bivalent vaccine contains HPV 16 and 18.

Approved indications of vaccinations for women;

- Cervical, vaginal, vulvar cancer
- Genital warts
- CIN 1-2-3
- Cervikal adenocarcinoma in situ

Approved indications for men are;

- Anal warts
- Anal cancer

The main goal of HPV vaccines is to vaccinate children aged 11-12 years. Preferably, vaccination should be done before sexual activity begins, before encountering HPV, so that the effectiveness of the vaccine increases. As for the compensatory vaccination, it should be carried out in women aged 13-26 years and men aged 13-21 years, and adults aged 27-45 years who might be at risk of new HPV infection and benefit from vaccination (Basel, 2021). Before vaccination, it is not necessary to take a cervical smear, the presence of HPV infection and a pregnancy test (Markowitz et al. 2014). Although this is our main preference, HPV vaccine has been shown to reduce recurrences even in patients infected with HPV who develop CIN (Kang et al 2013).

It is recommended to administer 2 doses of HPV vaccines between the ages of 9 and 14, and 3 doses from the age of 14. Since the presence of immune memory has been shown to persist after 5 years, there is no need for a repeat dose.

Since there is not enough data, vaccination should not be started during pregnancy. However, in people who accidentally got the HPV vaccine while pregnant; there was no difference in the incidence of spontaneous abortion, late fetal death and congenital anomaly (FDA 2014). But vaccination with HPV in pregnancy is contraindicated.

REFERENCES

Appleby, P., Beral, V., Berrington de González, A., Colin, D., Franceschi, S., Goodhill, A., ... & Sweetland, S. (2007). Cervical cancer and hormonal contraceptives: collaborative reanalysis of individual data for 16,573 women with cervical cancer and 35,509 women without cervical cancer from 24 epidemiological studies Lancet 370: 1609-1621, 2007. *PMID, 17993361*, 61684-5.

Kamolratanakul, S., & Pitisuttithum, P. (2021). Human Papillomavirus Vaccine Efficacy and Effectiveness against Cancer. *Vaccines*, *9*(12), 1413. https://doi.org/10.3390/vaccines9121413

Burchell, A. N., Winer, R. L., de Sanjosé, S., & Franco, E. L. (2006). Epidemiology and transmission dynamics of genital HPV infection. *Vaccine*, *24*, S52-S61.Castle PE etoli Long-term pensistance of prevalently detected humanu papillama virüs dafections in the absence of detectable cervical precancer and cancer. *J Infect Dis* 2011;203(6):814-22

De Sanjose, S., Bosch, F. X., Munoz, N., & Shah, K. (1997). Social differences in sexual behaviour and cervical cancer. *IARC scientific publications*, (138), 309-317.

de Villiers, E. M. (2013). Cross-roads in the classification of papillomaviruses. *Virology*, *445*(1-2), 2-10.

Dillner, J., Rebolj, M., Birembaut, P., Petry, K. U., Szarewski, A., Munk, C., ... & Iftner, T. (2008). Long term predictive values of cytology and human papillomavirus testing in cervical cancer screening: joint European cohort study. *Bmj*, *337*.

Doorbar, J., Quint, W., Banks, L., Bravo, I. G., Stoler, M., Broker, T. R., & Stanley, M. A. (2012). The biology and life-cycle of human papillomaviruses. *Vaccine*, *30*, F55-F70.

Food and Drug Administration. Highlights of prescribing information. Cervarix (human papillomavirus bivalent vaccine , recombinant). Silver Spring, MD: US Deparment of Health and Human Services; Food and Drug Administration, 2009.

Griffith WF: Preinvasive Lesions of the Lower Genital Tract. In: Hofmann BL, Schorge JO, Bradshaw KD, Halvorson LM, Schaffer JI, Corton MM, Williams GYNECOLOGY, 3rd ed, Dallas, McGraw-Hill Education, 2016, p.624-65

Gultekin, M., Zayifoglu Karaca, M., Kucukyildiz, I., Dundar, S., Boztas, G., Semra Turan, H., ... & Sencan, I. (2018). Initial results of population based cervical cancer screening program using HPV testing in one million T urkish women. *International journal of cancer*, *142*(9), 1952-1958.

Hill E. K. (2020). Updates in Cervical Cancer Treatment. *Clinical obstetrics and gynecology*, *63*(1), 3–11. https://doi.org/10.1097/GRF.0000000000000507

Hopkins, M. P. (2000). Adenocarcinoma in situ of the cervix--the margins must be clear. *Gynecologic oncology*, *79*(1), 4-5.

Kang, W. D., Choi, H. S., & Kim, S. M. (2013). Is vaccination with quadrivalent HPV vaccine after loop electrosurgical excision procedure effective in preventing recurrence in patients with high-grade cervical intraepithelial neoplasia (CIN2–3)? *Gynecologic oncology*, *130*(2), 264-268.

Keskin, D. D. (2018). Colposcopy results in Smear negative, High-risk HPV positive patients. *Medical Laboratory Technology Journal*, *4*(2), 43-48.

Landoni, F., Zanagnolo, V., Lovato-Diaz, L., Maneo, A., Rossi, R., Gadducci, A., ... & Ravanelli, K. (2007). Ovarian metastases in early-stage cervical cancer (IA2–IIA): a multicenter retrospective study of 1965 patients (a Cooperative Task Force study). *International Journal of Gynecological Cancer*, *17*(3), 623-628.

Massad LS; Preinvasive Disease of the Cervix In: Disaia PJ, Creasman WT, Mannel RS , McMeekin DS, Murch DG, CLINICAL GYNECOLOGİC ONCOLOGY, 9th ed, Philadelphia , Elsevier , 2018, p.1-19

Mayrand, M. H., Duarte-Franco, E., Coutlée, F., Rodrigues, I., Walter, S. D., Ratnam, S., ... & CCCaST Study Group. (2006). Randomized controlled trial of human papillomavirus testing versus Pap cytology in the primary screening for cervical cancer precursors: design, methods and preliminary accrual results of the Canadian cervical cancer screening trial (CCCaST). *International journal of cancer*, *119*(3), 615-623.

Nasiell, K., Roger, V., & Nasiell, M. (1986). Behavior of mild cervical dysplasia during long-term follow-up. *Obstetrics and gynecology*, *67*(5), 665-669.

Nicol, A. F., Andrade, C. V., Russomano, F. B., Rodrigues, L. L. S., Oliveira, N. S., & Provance Jr, D. W. (2016). HPV vaccines: a controversial issue? *Brazilian Journal of Medical and Biological Research*, *49*.

Petca, A., Borislavschi, A., Zvanca, M.E., Petca, R., Sandru, F., & Dumitrascu, M.C. (2020). Non-sexual HPV transmission and role of vaccination for a better future (Review). Experimental and Therapeutic Medicine, 20, 186. https://doi.org/10.3892/etm.2020.9316

Prendiville W, Sankaranarayanan R. Colposcopy and Treatment of Cercival Precancer. IARC Technical Publication No. 45.2017

Randall, M. E., Fracasso, P. M., Toita, T., Tedjarati, S. S., & Michael, H. (2013). Cervix. *Barakat R, Berchuck A, Markman M, Randall M. Principles and practice of gynecologic oncology. 6th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins*.

Saslow, D., Solomon, D., Lawson, H. W., Killackey, M., Kulasingam, S. L., Cain, J., ... & Myers, E. R. (2012). American Cancer Society, American Society for

Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *American journal of clinical pathology*, *137*(4), 516-542.

Serrano, B., Brotons, M., Bosch, F. X., & Bruni, L. (2018). Epidemiology and burden of HPV-related disease. *Best practice & research Clinical obstetrics & gynaecology*, *47*, 14-26.

Sethi, S., Müller, M., Schneider, A., Blettner, M., Smith, E., Turek, L., ... & Chang-Claude, J. (1998). Serologic response to the E4, E6, and E7 proteins of human papillomavirus type 16 in pregnant women. *American journal of obstetrics and gynecology*, *178*(2), 360-364.

Shepherd, J. H., Spencer, C., Herod, J., & Ind, T. E. J. (2006). Radical vaginal trachelectomy as a fertility-sparing procedure in women with early-stage cervical cancer—cumulative pregnancy rate in a series of 123 women. *BJOG: An International Journal of Obstetrics & Gynaecology*, *113*(6), 719-724.

Siegel, R., DeSantis, C., Virgo, K., Stein, K., Mariotto, A., Smith, T., ... & Ward, E. (2012). Cancer treatment and survivorship statistics, 2012. *CA: a cancer journal for clinicians*, *62*(4), 220-241.

Sung, H. Y., Kearney, K. A., Miller, M., Kinney, W., Sawaya, G. F., & Hiatt, R. A. (2000). Papanicolaou smear history and diagnosis of invasive cervical carcinoma among members of a large prepaid health plan. *Cancer*, *88*(10), 2283-2289.

Vergote, I., Van der Zee, A. G., Kesic, V., Sert, B., Robova, H., Rob, L., ... & Jacobs, I. (2007). ESGO statement on cervical cancer vaccination. *Int J Gynecol Cancer*, *17*(6), 1183-1185.

Vink, M. A., Bogaards, J. A., van Kemenade, F. J., de Melker, H. E., Meijer, C. J., & Berkhof, J. (2013). Clinical progression of high-grade cervical intraepithelial neoplasia: estimating the time to preclinical cervical cancer from doubly censored national registry data. *American journal of epidemiology*, *178*(7), 1161-1169.

Walboomers, J. M., Jacobs, M. V., Manos, M. M., Bosch, F. X., Kummer, J. A., Shah, K. V., ... & Muñoz, N. (1999). Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *The Journal of pathology*, *189*(1), 12-19.

Zhou, J., Sun, X. Y., Stenzel, D. J., & Frazer, I. H. (1991). Expression of vaccinia recombinant HPV 16 L1 and L2 ORF proteins in epithelial cells is sufficient for assembly of HPV virion-like particles. *Virology*, *185*(1), 251-257.

Zur Hausen, H. (2002). Papillomaviruses and cancer: from basic studies to clinical application. *Nature reviews cancer*, *2*(5), 342-350.

CHAPTER 11

YESTERDAY, TODAY AND TOMORROW OF BIRTH

Res. Asst. Okay ALPTEKİN[1]
Assoc. Prof. Dr. Deha Denizhan KESKİN[2]
Assoc. Prof. Dr. Seda KESKİN[3]

[1] Ordu University, Faculty of Medicine, Obstetrics and Gynecology Department, Ordu, Turkey okayalptekin@gmail.com, ORCID ID 0000-0001-6404-4158
[2] Ordu University, Faculty of Medicine, Obstetrics and Gynecology Department, Ordu, Turkey dehadenizhankeskin@gmail.com, ORCID ID 0000-0002-6108-7619
[3] Ordu University, Faculty of Medicine, Obstetrics and Gynecology Department, Ordu, Turkey adesniksek@gmail.com,ORCID ID 0000-0002-5640-4552

INTRODUCTION

The history of vaginal delivery begins with the existence of humanity. Cesarean section, which is a surgical delivery method, has been recorded in history since ancient times. The term cesarean section was first used in obstetrics in the 17th century. In this section, the history, development, methods, rates, and suggestions for recovery of delivery, which is as old as human history and sacred to humanity, will be examined.

1. VAGINAL DELIVERY

There are many practices related to vaginal birth from ancient times to the present. Although some of them have been abandoned, they have historical significance. Today, some applications that are still being questioned are wanted to be added to the current practice.

1.1. Anatolian Folk Culture

Turkey has experienced great migrations due to its geopolitical position, and as a region where various cultures are fused, it has been under the influence of great civilizations. Traces of the past are also encountered in some obstetric practices that develop as a result of this effect.

In Anatolian folk culture, pregnant women were given water prepared with the herb called “The Hand of the Virgin Mary” to reduce labor pains. In addition, other practices included opening closed places and locked things, untying the woman's knitting, emptying water-filled containers, and releasing caged birds and poultry (Başçetinçelik, 2001).

1.2. Antients Times, Chinese Medicine, Avicenna, Recent History

Acupuncture, a widely practiced method of Chinese medicine, has been used for over 5000 years to reduce labor pain and facilitate childbirth (Lee et al, 2004).

Soranus, a Greek physician who lived in the second century and specialized in gynecology, argued that the fetus could be removed from the mother's womb with some tools he developed to save the mother's life after trauma. Avicenna, a scholar who left his mark in the 10th century, was the first scientist to talk about forceps applications that could save the life of both the baby and the mother in difficult births (Das KN, 1929).

In 1813, years after Avicenna, the first example of modern forceps was accidentally discovered in an attic cabinet of a Hugh Chamberlen building (Simpsonet al 1849).

1.3. Cultural Effects and Various Methods

Birth, an important moment in the life of the parents, has been accepted as a happy event in all societies and has been a period in which many traditions were applied. Birth belts, amulets, the pregnant woman drinking the water with which she washes her hands or feet, and the husband untying the belt of the pregnant woman are just a few of these traditional customs (Köker, 1997).

Methods such as stimulating the nipple, pouring cold water on the head without the knowledge of the pregnant woman and making the pregnant woman drink milk or eat eggshell powder have been used in history to increase uterine contractions and accelerate labor in difficult births and are still being applied in some societies (Kalabak et al, 2003).

Grapes, almonds, and quince were fed to the pregnant woman during child birth to energize her. Before birth began, it was considered a common method for the woman not to have any knots on her, and to have the buttons and braids untied in her clothes (Artun, 1998).

In Thailand, it is believed that consuming green vegetables and drinking special herbal teas for three days, as well as saying any word that is believed to have a magical effect in previous deliveries, facilitates childbirth (Liamputtonget et al, 2005).

To ensure the separation of the placenta after birth, practices such as pressing on the belly of the woman giving birth with a broom, jumping up and down, opening her legs, and dipping into water vapor were performed. It was also believed that placing the embers wrapped in a clean cloth on the belly of the woman giving birth facilitated the separation of the placenta (Köker, 1997).

In a study examining the practices of village midwives, it was stated that practices such as pressing the pregnant woman's abdomen during labor and taking the pregnant woman up and down the stairs were frequently used to facilitate labor. In addition, in the same study, it was shown that the woman was also able to stand up and jump to facilitate the separation of the placenta. Despite this, it was stated in the study that besides beneficial maneuvers, there are situations that harm the baby and the mother (Şenol et al, 2004).

1.4. At present

Although many methods applied in ancient times have been abandoned, many applications that are still being used have survived to the present day.

1.4.1. Pushing

Nowadays, pregnant women are advised to listen to their bodies and instincts, rather than short-term spontaneous pushing or pushing methods taught in antenatal training. Although the use of pushing methods during vaginal delivery shortens the delivery time, the inclusion of different pushing techniques depends on patient compliance (de Tayrac et al, 2016).

1.4.2. Fundal pressure

Fundal pressure is the pressure applied manually or archally over the surface of the fundus to the birth canal to facilitate spontaneous vaginal delivery and prevent the prolongation of the second stage. The evidence for the benefits and harms of fundal pressure is insufficient and studies covering the effects on the maternal perineum and the safety of the baby are needed (Verheijenet al, 2009).

1.4.3. Perineal methods

It is aimed to facilitate childbirth and prevent perineal tears that may occur in vaginal births with methods such as perineal massage and perineal hot application. It is recommended to use lubricants dissolved in water when massaging the perineum. With these lubricants, it is recommended to massage the inner wall of the vagina with two fingers of both hands in an inverted C shape from lateral to medial. To prevent lacerations, the perineum must be supported by crowning the head of the newborn. With these applications, both episiotomy rates and perineal tears can be reduced (Asheimet al, 2011).

1.4.4. Upright Position

In most clinics, pregnant women spend their labor in a supine position. This misapplication reduces the effect of gravity on facilitating birth. In addition, both anterior-posterior and transverse outlets of the pelvis are narrowed in the lying position. Many studies have shown that the standing position has very beneficial effects on childbirth and, on the other hand, it provides a significant reduction in the rates of instrumental births and episiotomy (Guptaet al, 2012).

1.4.5. Episiotomy

Episiotomy is an incision made to the bulbocavernosus muscle of the perineum to prevent unwanted tears that may occur in the perineum during the birth of the baby's head. Today, it is routinely applied to avoid perineal tears. In the Cochrane systematic review, it was reported that limited episiotomy administration is more beneficial than a routine episiotomy. However, it may cause an increased risk of anterior perineal trauma (FIGO Guidelines, 2012).

1.4.6. Prophylactic oxygen

Prophylactic oxygen can be given to the pregnant woman to reduce the risk of labor with suspected fetal distress. However, the data on the application is insufficient (Fawole et al, 2012).

1.4.7. Tocolytic drugs

It is known that tocolytic agents used to delay preterm labor decrease myometrial contractions and increase placental circulation and fetal oxygenation. In addition, it should be kept in mind that this treatment (especially beta-mimetic drugs) may cause serious maternal cardiovascular side effects. In addition, there is insufficient evidence that the use of tocolytics reduces fetal distress (Hofmeyr et al, 2011).

1.4.8. Clamping of the umbilical cord

Numerous practices regarding the timing of attachment of the umbilical cord after birth have been discussed until today. Clamping of the umbilical cord, after waiting for at least 60 seconds after delivery and after cessation of cord beat, is defined as delayed cord clamping. Neonatal benefits of delayed cord clamping have been reported in some studies. However, in larger studies, it has been shown that both methods are applicable and there is no statistically significant difference between the methods in terms of maternal fetal morbidity and mortality (McDonald et al, 2013).

1.4.9. Removal of the placenta

Today, applications such as fundal pressure and controlled cord traction are still used to facilitate the delivery of the placenta. It has been reported that such procedures, which shorten the third stage of labor, reduce the risk of postpartum hemorrhage (Peña-Martíet al, 2007).

1.4.10. Uterotonic drugs

Uterotonic drugs, which are used in active labor and cause uterine contraction, are also used to reduce postpartum hemorrhage, especially in the third stage of labor. There are also studies on the timing of postpartum uterotonic use. There is no significant difference between the uterotonic treatments applied before or after the placenta is removed in terms of the amount of postpartum hemorrhage (Soltaniet al, 2010).

The World Health Organization's recommendations for the use of uterotonic drugs for the prevention of postpartum hemorrhages are indicated in the table (World Health Organization, 2021).

- The use of uterotonics for the prevention of PPH during the third stage of labour is recommended for all births (strong recommendation, moderate-quality evidence).
- Oxytocin (10 IU, IV/IM) is the recommended uterotonic drug for the prevention of PPH (Strong recommendation, moderate-quality evidence).
- In settings where oxytocin is unavailable, the use of other injectable uterotonics (e.g. ergometrine/ methyl ergometrine or the fixed drug

combination of oxytocin and ergometrine) or oral misoprostol (600 μg) is recommended (Strong recommendation, moderate-quality evidence).

- In settings where skilled birth attendants are not present and oxytocin is unavailable, the administration of misoprostol (600 μg PO) by community healthcare workers and lay health workers is recommended for the prevention of PPH (Strong recommendation, moderate-quality evidence).

2. CESAREAN DELIVERY (C-SECTION)

Cesarean section is etymologically based on the word 'lex caesare', which is the concept of removing the baby from the mother's womb. In Latin, it is derived from the word "caedere", which means to cut (Simpson et al, 1989).

2.1. Historical Process, Julius Caesar

Caesarean section is mentioned in mythology. The first written historical records about cesarean section belong to the Sumerians in 2000 BC (Durfee et al, 1993).

The purpose of cesarean delivery has evolved from the past to the present. While cultural reasons were at the forefront of saving the fetus in the past, today the health of both mother and newborn is taken into consideration. It is rumored in history that Julius Caesar was born by cesarean section. However, since Caesar's mother, Aurelia Cotta, is known to have lived for many years after birth, this possibility seems unlikely. In ancient times, cesarean section was used to save the fetus of a mother who was about to die in the perimortem period. As a scientific term, it was first used in cesarean obstetrics in the seventeenth century (Todaman, 2007).

2.2. High Mortality

In the Jewish literature, it is stated that cesarean section can be applied in case of irreversible life risk for the mother, but this surgical procedure is not performed very often. (Rosner, 1984).

The perinatal mortality rate was close to 100% in cesarean section operations performed in the past. Surgery only when near death, high infection rates (lack of cleanliness) and lack of a dissolving suture to suture the uterus are the main factors in this rate (Gupta, 2008).

2.3. First Success

The first successful cesarean was performed by Jacob Nufer in 1500 in Siegersasen, Switzerland. According to the records, Nufer performed this operation on his wife and gave birth to his child. In the details of this historical operation, it was recorded that the abdominal wall and uterus were cut with the help of a razor, the baby was taken out, then the bleeding was controlled with many stitches and the incisions were closed (Gupta, 2008).

2.4. First Research

The case of cesarean section, which was published for the first time in a scientific medical journal, was carried out by Trautmann in 1610. In this case, this operation was performed on a pregnant woman with a large abdominal hernia. The newborn survived after cesarean section, but the mother died on the 25th postpartum day despite the healing of the uterine wall. The crescent-shaped incision on the pubic bone, which is applied today, was first applied to a 9-month pregnant woman who was injured by a bull in the Netherlands in 1647 (Gupta, 2008).

2.5. Surgical Technique

2.5.1. Skin Incision

In ancient times, an abdominal incision was made on the right or left side, parallel to the linea alba. Afterward, it was noticed that the bleeding was less with the incision made in the midline along the linea alba and it started to be preferred more. From the beginning of the nineteenth century, the skin and fascia were cut transversely. This incision, which is the most frequently applied skin incision today, is known as the 'Pfannenstiel incision'. With this incision, which has better cosmetic results, postoperative pain is also less common (Lurie et al, 2003).

2.5.2. Uterine Incision

Throughout history, the uterine incision has been tried in various ways such as transverse, longitudinal and oblique.

2.5.2.1. First Methods

Lebas was the first surgeon to repair the uterine incision by suturing it in 1769. However, the suturing procedure did not reduce maternal deaths, most of which were due to sepsis. Johnson attempted a transverse incision into the lower uterine segment in 1786, and this method remained popular for many years (Boley et al, 1991).

In the 1800s, surgeons such as Ritgen, Physick, Blundell and Sanger suggested methods such as lateral extraperitoneal approach, midline incision, and suturing of the uterus outside the abdomen (Boley et al, 1991).

2.5.2.2. Kerr Method

Monro Kerr in 1926 made the lower uterine segment transverse incision with the idea of less bleeding, lower infection rate, and less uterine rupture in subsequent pregnancies, because it made the scar region stronger, and has become more popular than other operations (Lurie et al, 2003).

2.5.3. Porro Operation

In 1876, Eduardo Porro performed the peripartum hysterectomy, which is known by his name today. Due to the low sepsis rate of the technique, Porro has succeeded in greatly reducing maternal mortality (O'Sullivan1990).

2.5.4. Extraperitoneal Cesarean

Frank developed the extraperitoneal cesarean section method in 1907. This method was developed to prevent the spread of infection to the intraperitoneal area. In 1908, Hugo Selheim planned the uterine incision line to cover the lower segment of the uterus. The main idea is to prevent postoperative peritonitis and incisional hernia. After the Second World War, the use of antibiotics with a preventive and therapeutic effect significantly reduced the incidence of serious post-operative infections (Van Dongen, 2009).

2.6. Cesarean Section Rates In The World and In Turkey

The World Health Organization (WHO) has reported that the ideal acceptable cesarean section rate should be below 10-15%. Despite this, cesarean section rates continue to increase rapidly in developed and developing countries. According to the cesarean section rates, Turkey is among the first five countries in the world and the first among OECD countries (World Health Organization, 2015).

2.7. Benefits and Harms of Cesarean Section

No evidence performing a cesarean section when it is not necessary has any benefit for the mother and newborn. As with all surgeries, the cesarean section has short and long-term effects. Cesarean delivery is a procedure that should only be performed for medical reasons. Rates over 10% do not provide additional contributions to newborn health. Instead of making efforts to reach a certain rate in cesarean delivery rates, cesarean delivery service should be targeted at women in need (World Health Organization, 2015)

2.8. Cesarean Section Indications

The most common cesarean indication in the literature is repeated cesarean section. Later causes are pelvic dystocia, fetal distress and presentation anomalies, respectively (Kıymet et al 2018).

Cesarean indications:

1. **Maternal reasons:**
   - Cephalopelvic disproportion
   - Previous ceserean section
   - Eclampsia
   - Failed induction
   - Placenta previa
   - Severe pelvic inflammatory disease
   - Obstructed labor
2. **Fetal reasons:**
   - Fetal distress
   - Breech presentation
   - Macrosomia
   - Pregnancy complicated by multiple fetuses
   - Transverse position
   - Postdatism

2.9. Turkey Reports

According to the Turkey Health Statistics report; The primer cesarean rate in Turkey was 26.5% and the cesarean rate in all deliveries was reported as 54.4%. Cesarean section rates in Turkey have reached this level of 20% in the last 20 years. The main reasons for this increase are the intense medico legal pressure on the physician and the frequent application of cesarean section due to maternal demand (Ministry of Health of the Republic of Turkey, 2019).

2.10. Reasons for Increase and Suggestions For Reduction

Many associations operating in Turkey have made various suggestions regarding the rapidly increasing cesarean section rates. The obstetrics and gynecology community in Turkey is seriously disturbed by the medicolegal pressures on physicians in recent years and blames this pressure as responsible for the increasing cesarean section rates. Physician protective practices regarding this pressure must be resolved as soon as possible, both legally and administratively. Because the medico legal pressure on physicians is increasing defensive medicine practices.

The relationship between the Social Security Institution's service procurement from private hospitals and cesarean section rates should be questioned and necessary precautions should be taken. The Ministry of Health,

universities, non-governmental organizations and all institutions that can contribute to the solution of the problem should stand side by side.

The main goal should not be just “less cesarean section” but “more accurate delivery and delivery management”. The possibilities for labor analgesia should be expanded rapidly.

An external audit can be applied in clinics where cesarean section rates are very high. At this point, professional organizations and the Ministry of Health can work together. The accreditation process of clinics can also be used for external audit purposes. Informative booklets and brochures about vaginal birth and cesarean section should be prepared for pregnant women. Pregnant information classes should be created.

Trauma follow-up and delivery should be done in single-person delivery units, and one-on-one midwife-nurse support should be provided. Models defining minimum requirements for delivery rooms should be developed and these minimums should be made mandatory and checked over time (Turkish Maternal Fetal Medicine and Perinatology Society, 2018).

REFERENCES

Aasheim, V., Nilsen, A. B., Lukasse, M., &Reinar, L. M. (2011). Perineal techniques during the second stage of labor for reducing perineal trauma. Cochrane Database SystRev (12), Cd006672. https://doi.org/10.1002/14651858.CD006672.pub2

Aliye BULUT, Ç. Y., Fatma DEMIR. (2022). Traditional methods known and applied by women living in the city center of Bingol for mother and infant care [ResearchPaper]. 6. https://doi.org/https://dergipark.org.tr/tr/pub/estudamhsd/issue/60260/727868

Artun, E., (1998). Transition Periods in Tekirdağ Folk Culture, Birth-Marriage-Death, One, Journal of Turkish World Studies, 9-10; 85-1007.

Başçetinçelik, A. (2001). Birth, Marriage, Death, Kuvayi Milliye Festivals in and Around Karaisalı. Karaisalı fromPastto Present. Retrieved 22.08.2022 from http://turkoloji.cu.edu.tr/CUKUROVA/makaleler/bascetincelik_karaisali.pdf

Boley, J. P. (1991). The history of caesarean section. 1935. Cmaj, 145(4), 319-322.

de Tayrac, R., &Letouzey, V. (2016). Methods of pushing during vaginal delivery and pelvic floor and perineal outcomes: a review. Curr Opin Obstet Gynecol, 28(6), 470-476. https://doi.org/10.1097/gco.0000000000000325

F, R. (1984). Maimonides (1138-1204): Rabbi, Physician and Philosopher.

Fawole, B., &Hofmeyr, G. J. (2012). Maternal oxygen administration for fetal distress. Cochrane Database Syst Rev, 12(12), Cd000136. https://doi.org/10.1002/14651858.CD000136.pub2

FIGO Guidelines, S. M. a. N. H. S. C. (2012). Management of the second stage of labor. Int J Gynaecol Obstet, 119(2), 111-116. https://doi.org/10.1016/j.ijgo.2012.08.002

Gupta, J. K., Hofmeyr, G. J., &Shehmar, M. (2012). Position in the second stage of labor for women without epidural anaesthesia. Cochrane Database SystRev(5), Cd002006. https://doi.org/10.1002/14651858.CD002006.pub3

GuptaM. (2008). The Birth of Caesarean Section. University Of Western Ontario Medical Journal, 78(1), 79-85.

H., K. k. A. (1997). Birth and midwifery history Birth and Midwifery History Congress, Kayseri.

J. A. Simpson, E. S. C. W. (1989). Theo xford english dictionary (2nd ed.). Oxford University Press.

JE, S. (1993). Cesarian Section -- A Brief History. InA.C.o. o.a. Gynecologists (Ed.), A brochure to accompany an exhibition on the history of cesarean section at the National Library of Medicine (pp. 30).

JY, S. (1849). On a suction-tractor; or new mechanical power, as a substitute for the forceps in tedious labors. . Edinburgh Monthly J MedSci, 32, 556-558.

Kalabak, A., Urfalıoğlu, A. (2003). Alternative Approaches to Women's Health. Journal of Obstetrics and Gynecology, 1(4), 244-250.

Kıymet YEŞİLÇİÇEK ÇALIK, R. E., Özlem KARABULTLU. (2022). Rates and indications of 4-year cesarean deliveries in a tertiary hospital [RESEARCH ARTICLES]. 5. https://doi.org/https://dergipark.org.tr/tr/pub/hsp/issue/36209/411299

KN, D. (1929). Obstetric Forceps: Its History and Evolution. The Indian Medical Gazette, 64, 407 - 408.

Lee, H., &Ernst, E. (2004). Acupuncture for labor pain management: A systematic review. American Journal of Obstetrics& Gynecology, 191(5), 1573-1579. https://doi.org/10.1016/j.ajog.2004.05.027

Liamputtong, P., Yimyam, S., Parisunyakul, S., Baosoung, C., &Sansiriphun, N. (2005). Traditional beliefs about pregnancy and child birth among women from Chiang Mai, Northern Thailand. Midwifery, 21(2), 139-153. https://doi.org/10.1016/j.midw.2004.05.002

Lurie, S., &Glezerman, M. (2003). The history of cesarean technique. Am J Obstet Gynecol, 189(6), 1803-1806. https://doi.org/10.1016/s0002-9378(03)00856-1

M., G. (2008). The Birth of Caesarean Section. University of Western Ontario Medical Journal, 78(1), 79-85.

McDonald, S. J., Middleton, P., Dowswell, T., & Morris, P. S. (2013). Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. Cochrane Database SystRev, 2013(7), Cd004074. https://doi.org/10.1002/14651858.CD004074.pub3

Directorate, T. C. S. B. S. B. S. G. (2019). Health Statistics Yearbook 2019 News Bulletin Retrieved 22.08.2022 from https://sbsgm.saglik.gov.tr/TR,73329/saglik-istatistikleri-yilligi-2019-haber-bulteni-yayimlanmistir.html

O'Sullivan, J. F. (1990). Caesarean birth. Ulster Med J, 59(1), 1-10.

Peña-Martí, G., &Comunián-Carrasco, G. (2007). Fundal pressure versus controlled cord traction as part of the active management of the third stage of labor. Cochrane Database SystRev, 2007(4), Cd005462. https://doi.org/10.1002/14651858.CD005462.pub2

R., D. (1993). Cesarean section. In Nichols HN (Ed) Gynecologic and Obstetric Surgery (pp. 1075-1122). Mosby-Year BookInc.

Rosner, F. (2016). Jewish Medicine in the Talmudic Period. In H. Wolfgang (Ed.), Band 37/3. Teilband Philosophie, Wissenschaften, Technik. Wissenschaften (Medizinund Biologie [Forts.]) (pp. 2866-2894). De Gruyter. https://doi.org/doi:10.1515/9783110809008-016

Soltani, H., Hutchon, D. R., &Poulose, T. A. (2010). Timing of prophylactic uterotonics for the third stage of labour after vaginal birth. Cochrane Database of Systematic Reviews(8). https://doi.org/10.1002/14651858.CD006173.pub2

Statement, T. M. F. M. a. P. S. t. N. C. P. (2018, 02.11.2018). Cesarean Section Rates in Turkey: Why are they increasing? How can we lower it? Turkish Maternal Fetal Medicine and Perinatology Society Retrieved 22.08.2022 from https://www.tmftp.org/files/bildiriler/turkiyede-sezaryen-oranlari-paneli-sonuc-bildirisi-15112018.pdf

Todman, D. (2007). A history of caesarean section: from ancient world to the modern era. Aust N Z J Obstet Gynaecol, 47(5), 357-361. https://doi.org/10.1111/j.1479-828X.2007.00757.x

Van Dongen, P. (2009). Caesarean section–etymology and early history. South African Journal of Obstetrics and Gynaecology, 15(2), 62-66.

Verheijen, E. C., Raven, J. H., &Hofmeyr, G. J. (2009). Fundal pressure during the second stage of labour. Cochrane Database Syst Rev(4), Cd006067. https://doi.org/10.1002/14651858.CD006067.pub2

World Health, O. (2021). WHO recommendation on uterine balloon tamponade for the treatment of postpartum haemorrhage. World Health Organizati on. https://apps.who.int/iris/handle/10665/340796

CHAPTER 12

SHOULDER GIRDLE ASSESSMENT AND CLINICAL TAPING TECHNIQUES

Asst. Prof. Dr. Halil YILMAZ[1]

[1]Ordu University, Medicine Faculty, Department of Anatomy Ordu, TÜRKİYE. halilyilmaz@gmail.com, Orcid ID: 0000-0002-8234-4901

INTRODUCTION

Composed of 4 joints, the shoulder is a complex structure with a wide range of motion and high functional functions. To understand the cause of shoulder pathologies, it is very important to analyze the relationship network of muscle, joint, bone and neurovascular structures with each other and within themselves. The physical examination decision is important in the diagnosis and evaluation of patients with shoulder complaints. For the shoulder, general physical examination such as palpation, range of motion, muscle strength, neurological and vascular examination, as well as special physical examination tests such as structural stability and integrity tests, have a very important place in clinical decision making (Bakhsh & Nicandri, 2018).

Shoulder Girdle

The shoulder girdle consists of the connections between the scapula, humerus, and the clavicle. The landmarks of the scapula are the supraspinous and infraspinous fossa separated by the coracoid process superiorly, the glenoid space laterally, the subscapular fossa anteriorly, and the spine of scapula posteriorly (Huegel, Williams, & Soslowsky, 2015). The clavicle resembles the letter S and lies almost horizontally between the sternum and the acromion. The sternal end joins the sternoclavicular joint, and the acromial end joins the acromioclavicular joint.

The structure that connects the upper extremity to the trunk is called the shoulder girdle. The clavicle and scapula form the bony skeleton of the shoulder girdle. There are 3 anatomical (sternoclavicular joint, coracoclavicular joint, glenohumeral joint) and 1 physiological (scapulothoracic joint) 4 joints in which these two bones are located.

Sternoclavicular Joint

It is a flood type joint between the clavicular articular surface of the sternum and the sternal articular surface of the clavicle. There is an intraarticular disc to ensure the harmony between the articular surfaces. Although there is little bone stability in this joint, it is one of the most stable joints in the body due to the wide and strong ligaments, and dislocations are very rare. The sternoclavicular joint is the only anatomical joint that connects the upper extremity to the trunk (Table 1) (Monaro, 2015).

Table 1. Movement of acromioclavicular joint

Movement	Muscle	Origin	Insertion	Innervation
Shoulder protraction	Serratus anterior	Superior part: Ribs 1-8 and external oblique muscle	Anterior surface of superior angle, medial border and inferior angle	Long thoracic nerve (C5- C7)
	Pectoralis major	Clavicular part: Anterior surface of medial half of clavicle	Crest of greater tubercle of humerus	Lateral pectoral nerves (C5-T1
		Sternocostal part: Anterior surface of sternum, Costal cartilages of ribs 1-6		
		Abdominal part: Anterior layer of rectus sheath		
	Pectoralis minor	Ribs 3-5's costal cartilage	Coracoid process of scapula	Medial pectoral nerves (C5-T1)
Shoulder retraction	Trapezius (Middle part)	Middle part: Spinous processes of vertebrae T1-T4	Middle part: Acromion	Accessory nerve (CN XI)
	Rhomboid minor	Spinous processes of vertebrae C7-T1	Root of spine of scapula	Dorsal scapular nerve (C4-C5)
	Rhomboid major	Spinous process of vertebrae T2-T5	Medial border of scapula	Dorsal scapular nerve (C4-C5)
	Latissimus dorsi	Spinous processes of vertebrae T7-T12, Thoracolumbar fascia, posterior crest of ilium, ribs 9-12	Intertubercular groove of the humerus	Thoracodorsal nerve (C6-C8)
Shoulder elevation	Trapezius (superior part)	Superior part: External occipital protuberance, nuchal ligament	Superior part: 1/3 distal part of clavicle	Accessory nerve (CN XI)
	Levator scapulae	Transverse processes of C1 - C4 vertebrae	Superior angle of scapulae	C3-C4, Dorsal scapular nerve
	Rhomboid minor	Spinous processes of vertebrae C7-T1	Root of spine of scapula	Dorsal scapular nerve (C4-C5)
	Rhomboid major	Spinous process of vertebrae T2-T5	Medial border of scapula	Dorsal scapular nerve (C4-C5)
Shoulder depression	Trapezius (Inferior part)	Inferior part: Spinous processes of vertebrae T4-T12	Inferior part: Scapular spine	Accessory nerve (CN XI)
	Rhomboid minor	Spinous processes of vertebrae C7-T1	Root of spine of scapula	Dorsal scapular nerve (C4-C5)
	Rhomboid major	Spinous process of vertebrae T2-T5	Medial border of scapula	Dorsal scapular nerve (C4-C5)

Acromioclavicular joint

This joint formed between the acromion of the scapula and the acromial facet of the clavicle is divided into two by the articular disc. Increase relative to the convex articular surface. It is a planar type and can make a sliding motion. In injuries of this joint, the Rockwood classification system is used, and young men are more affected. The joint plane is typically inclined 20°–30°. The acromioclavicular joint is small, averaging 9 mm in height and 19 mm in length (Flores, Goes, Gómez, Umpire, & Pathria, 2020).

Glenohumeral (Shoulder) joint

The glenohumeral joint is increased relative to the convex articular surface. It is a spheroid (ball-socket) type joint between the humeral head and the glenoid cavity. Although this joint provides the widest range of motion of the body, its stabilization is quite weak (Ladd, Crews, & Maertz, 2021). The main reasons for poor stabilization are loose joint capsule and incompatibility between humeral head and glenoid cavity. To reduce this mismatch, the labrum glenoid cavity wraps the articular surface of the glenoid all around (Lugo, Kung, & Ma, 2008). The action of the muscles is very important to prevent dislocation. These stabilizing muscles are called rotator cuff muscles. Outside the joint capsule, there are glenohumeral ligament, coracohumeral ligament, transverse humeral ligament. Since there are many muscles that move the joint, there are structures called bursae to reduce friction between the muscles. There are 8 bursae in the glenohumeral joint, and the most important ones in terms of clinical medicine are subacromial and subscapular bursa.

The glenohumeral joint enables the arm to perform abduction-adduction in the sagittal axis, flexion-extension in the transverse axis, and internal and external rotation in the vertical axis (Table 2) (Lugo et al., 2008).

Table 2. Movement of glenohumeral joint

Movement	Muscle	Origin	Insertion	Innervation
Shoulder flexion	Deltoid (clavicular part)	1/3 lateral part of clavicle	Deltoid tuberosity	Axillary nerve (C5-C6)
	Pectoralis major (Clavicular)	Anterior surface of medial half of clavicle	Crest of greater tubercle of humerus	Lateral pectoral nerves (C5-T1)
	Biceps brachii	Long head: Supraglenoid tubercle of the scapula Short head: Coracoid process	Radial tuberosity	Musculocutaneous nerve (C5-C6)
	Coracobrachialis	Coracoid process	Anteromedial of humerus shaft	Musculocutaneous nerve (C5-C7)
Shoulder extension	Latissimus dorsi	Spinous processes of vertebrae T7-T12, Thoracolumbar fascia, posterior crest of ilium, ribs 9-12	Intertubercular groove of humerus	Thoracodorsal nerve (C6-C8)
	Teres major	Lower part of the lateral edge of the scapula	Intertubercular groove of humerus	Lower subscapular nerve (C5-C7)
	Teres minor	Lateral edge of scapula	Greater tubercle of humerus	Axillary nerve (C5-C6)
	Deltoid (spinal part)	Spine of Scapula	Deltoid tuberosity	Axillary nerve (C5-C6)
Shoulder abduction	Supraspinatus (0-20^0)	Supraspinous fossa	Greater tubercle of humerus	Suprascapular nerve (C5, C6)
	Deltoid (Acromial part)	Acromion	Deltoid tuberosity	Axillary nerve (C5-C6)
	Trapezius (superior part)	External occipital protuberance, nuchal ligament	1/3 distal part of clavicle	Accessory nerve (CN XI)
	Serratus anterior	Superior part: Ribs 1-8 and external oblique muscle	Anterior surface of superior angle, medial border and inferior angle	Long thoracic nerve (C5- C7)
Shoulder adduction	Pectoralis major (Sternocostal)	1-6 Ribs of costal cartilage	Crest of greater tubercle	Lateral pectoral nerves (C5-T1
	Latissimus dorsi	Spinous processes of vertebrae T7-T12, Thoracolumbar fascia, posterior crest of ilium, ribs 9-12	Intertubercular groove of humerus	Thoracodorsal nerve (C6-C8)
	Teres major	Lower part of the lateral edge of the scapula	Intertubercular groove of humerus	Subscapular nerve (Lower) (C5-C7)
	Triceps (Long head)	Infraglenoid tubercle	Olecranon	Radial nerve (C6-C8)
	Coracobrachialis	Coracoid process	Anteromedial of humerus shaft	Musculocutaneous nerve (C5-C7)
Shoulder lateral rotation	Teres minor	Lateral edge of scapula	Greater tubercle of humerus	Axillary nerve (C5-C6)
	Infraspinatus	Infraspinous fossa	Greater tubercle of humerus	Suprascapular nerve (C5, C6)
Shoulder medial rotation	Teres major	Lower part of the lateral edge of the scapula	Intertubercular groove	Lower subscapular nerve (C5-C7)
	Pectoralis major	Clavicular part: Medial half of clavicle		
		Sternocostal part: Sternum, ribs 1-6 of costal cartilage	Crest of greater tubercle	Lateral pectoral nerves (C5-T1)
		Abdominal part: Rectus sheath		
	Subscapularis	Subscapular fossa	Lesser tubercle of humerus	Subscapular nerves (C5 - C6)
	Latissimus dorsi	Spinous processes of vertebrae T7-T12, Thoracolumbar fascia, posterior crest of ilium, ribs 9-12	Intertubercular groove of the humerus	Thoracodorsal nerve (C6-C8)
	Deltoid (clavicular part)	1/3 lateral part of clavicle	Deltoid tuberosity	Axillary nerve (C5-C6)

The list of muscles of shoulder girdle

Trapezius

Levator scapulae

Rhomboids

Serratus anterior

Pectoralis minor (Oh, Park, & Rhee, 2018)

Apart from the shoulder girdle muscles, there are 6 scapulohumeral muscles. 4 of these muscles are the muscles that strengthen the glenohumeral joint and are known as the rotator cuff muscles. Rotator cuff muscles; supraspinatus, infraspinatus, teres minor and subscapularis muscles. Since the stabilization of the glenohumeral joint is weak due to its structure, the rotator cuff muscles play an important role in providing joint stabilization (Oh, Park, & Rhee, 2018). Although teres major muscle and deltoid muscle are included in scapula humeral muscles, they are not rotator cuff muscles.

Supraspinatus muscle: It is known that the most affected muscle in rotator cuff tears is the supraspinatus muscle (Mochizuki et al., 2008). Subacromial bursitis or subacromial impingement is the most common cause of shoulder pain. Subacromial impingement syndrome causes shoulder pain when the thickened bursa compresses the supraspinatus tendon in difficult elevations. Pain occurs when initiating resistive arm abduction (Şenbursa & Atay, 2011). The empty can test is used in the diagnosis of supraspinatus impingement syndrome. **Empty can test:** In the seated patient, the glenohumeral joint is passively brought to 90° of abduction. While the patient's arm is placed in full internal rotation, arm flexion is also reduced to 60°. The therapist places his hand 5 cm above the patient's elbow joint and asks him to abduct against resistance. If the patient feels pain, it is considered to have supraspinatus impingement syndrome (Figure 1) (Iwata et al., 2017).

Figure 1. Empty Can test for supraspinatus tendinitis

Infraspinatus muscle: The infraspinatus muscle is the rotator cuff muscle that begins at the medial 2/3 of the infraspinous fossa and ends at the greater tubercle. In addition to external rotation of the arm, it takes part in the stabilization of the glenohumeral joint and it is innervated by the suprascapular nerve (Yanase et al., 2018). The infraspinatus spring back test is used in the diagnosis of infraspinatus impingement. **Infraspinatus spring back test:** By holding the wrist of the patient sitting in the chair, the arm is passively brought to 90° of flexion, the forearm to 90° flexion and the arm to full external rotation. The patient is asked to maintain this position. Failure of the patient to maintain position indicates an infraspinatus or reverse minor muscle tear (Figure 2) (Hughes, Green, & Taylor, 2014).

Figure 2. Spring back test for infraspinatus tendinitis

Subscapularis muscle: It begins by filling the fossa subscapularis and at the lateral edge of the scapula and ends at the lesser tubercle. Its primary task is to internally rotate the arm, in addition to increasing the stabilization of the glenohumeral joints, and It is innervated by the subscapular nerve. The Gerber (lift-off) test is used to test for subscapularis muscle damage. **Gerber test:** In this test, the patient is asked to stand. The patient brings the arm in extension, external rotation brings the forearm to 80° of flexion and puts the back of the hand on the lumbar vertebrae. The patient is asked to move his hand back and away from his back. Failure of the test indicates subscapular tendon damage (Figure 3) (Micheroli et al., 2015).

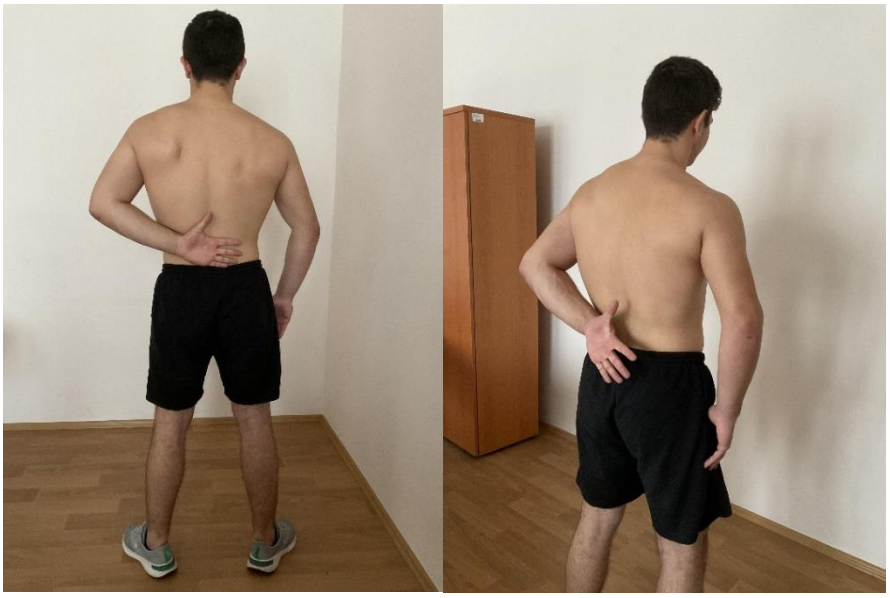


Figure 3. Gerber test for subscapular tendinitis

Teres minor muscle: Teres minor muscle starts from the upper 2/3 of the lateral border of the scapula and ends in the lower part of greater tubercle. The function of the teres minor muscle is to strengthen the glenohumeral joint, in addition to external rotation and slight adduction of the arm. Pathology of the teres minor muscle is tested with the Hornblower sign test. **Hornblower sign test:** While the patient is sitting or standing, the patient's arm is abducted 90° by the therapist. The patient is asked to flex the forearm to 90°. The patient is asked to externally rotate the arm against resistance. If the patient cannot bring the arm to external rotation, it is decided that there is a teres minor pathology (Jain et al., 2017).

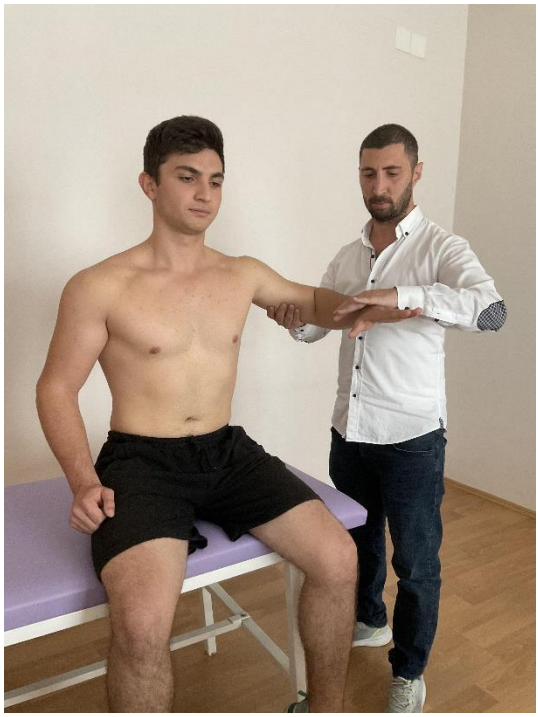


Figure 4. Hornblower sign test for teres minor pathology

The deltoid muscle and teres major muscle are included in the humeral muscle group of the scapula and not among the rotator cuff muscles.

Teres major muscle: This muscle starts from the lower 1/3 of the lateral edge of the scapula, just below the teres minor muscle, and ends at the crest of lesser tubercle in the humerus. Its main function is internal rotation of the arm, and it assists in adduction and extension of the arm. İt is innervated by the subscapular nerve. Patte test is applied for reverse major pathologies. **Patte test:** In the Patte test, the patient's arm is placed in 90° abduction and 90° forearm flexion in the scapular plane by the therapist. The patient's arm is neutral in rotation. The patient is asked to turn his arm into external rotation from this position against the therapist's resistance. (Figure 5)

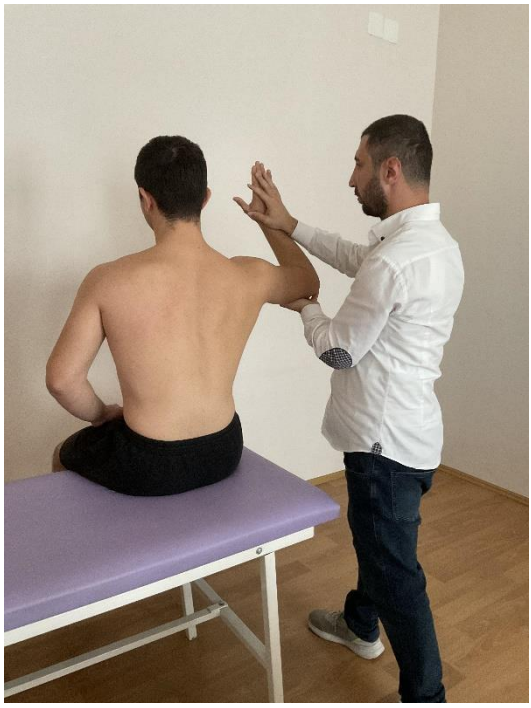


Figure 5. Patte test for teres major tendinopathy

Deltoid muscle: The deltoid muscle, unique to humans, is a triangular muscle. The anterior part of the muscle is known as the clavicular part, from the outer 1/3 of the clavicle; the acromial part forming the middle part of the muscle is from the acromion; the spinal part, which forms the posterior part of the muscle, originates from the spine of scapula. In these three parts, it terminates at the deltoid tuberosity. The common function of the three parts is to abduct the arm between 20-90°. The specific tasks of these parts are clavicular part arm internal rotation and flexion, acromial part arm abduction, spinal part arm external rotation and extension. This muscle is innervated by the axillary nerve.

Although not technically a part of the rotator cuff muscles, the long head of the biceps brachii muscle functions as a functional part of this muscle group because it passes through the glenohumeral joint (Virk & Cole, 2016). Tendinopathy, which occurs in the long head of the biceps brachii, has a wide clinical picture. Biceps long head tendinopathies in addition to other shoulder pathologies are frequently encountered in clinics. The Yergason test is used in clinical judgment of biceps long head tendinopathies. **Yergason test:** While the patient is sitting or standing, the therapist is positioned next to the patient. The patient's forearm is passively flexed to 90°. The therapist grasps the forearm

with one hand and the shoulder with the other. The patient is asked to resist this resistance as the therapist forces the forearm to external rotation at the glenohumeral joint. If it is a long head tendinopathy of the biceps muscle, the patient will have a feeling of pain. Observationally, it can be noticed that the tendon is unstable in the intertubercular groove (Venessa 2011).

Figure 6. Yergason test for deltoid muscle damage

Clinical taping application of supraspinatus muscle

Tape shape and length: In the clinical taping of the supraspinatus muscle, a 5 cm Y-shaped strip tape is applied with the inhibition technique.

Positioning: The patient's arm is internally rotated, and the shoulder is protracted. The head is lateral flexed to face the opposite shoulder.

Intervention technique: The base part of the Y-shaped strip tape is adhered to 2 fingers under the greater tubercle by %15-25 stretching. The upper arm of the Y-shaped tape is applied to the junction of the upper part of the trapezius muscle and the middle part of the tape, without stretching, up to the medial edge of the scapula. The lower arm of the Y-shape tape is applied along the supraspinous fossa up to the medial edge of the scapula without stretching (Figure 7) (de Oliveira, de Fontenay, Bouyer, Desmeules, & Roy, 2017).

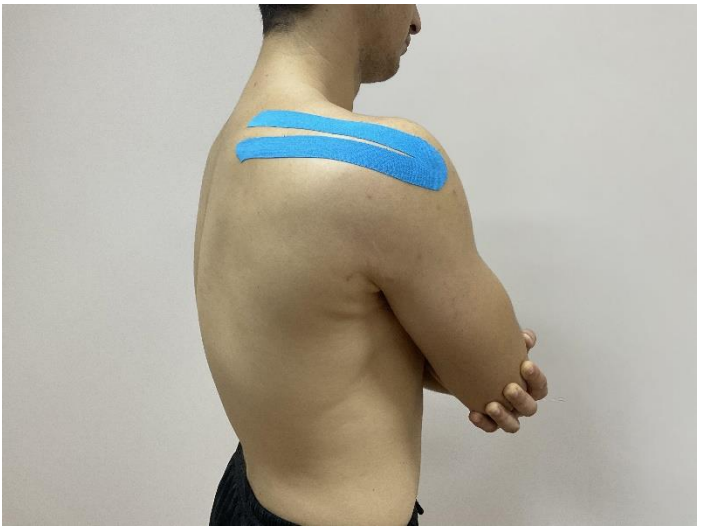


Figure 7. Clinical taping for supraspinatus muscle

Clinical taping application of infraspinatus muscle

Tape shape and length: In the clinical taping of the infraspinatus muscle, a 5 cm Y-shaped tape is applied with the inhibition technique.

Positioning: The patient's arm is internally rotated, and the shoulder is protracted.

Intervention technique: The base of the Y-shaped tape is started to be applied 2 fingers below the greater tubercle. The tape is stretched up to two times. The upper arm of the Y-strip tape is adhered without stretching, following the lower edge of the spine of scapula, up to the medial edge of the scapula. The Y-shaped tape is applied to the lower arm of the tape along the lower edge of the infraspinatus muscle up to the medial edge of the scapula without stretching (Figure 8)(Smith, Hotze, & Tate, 2021).

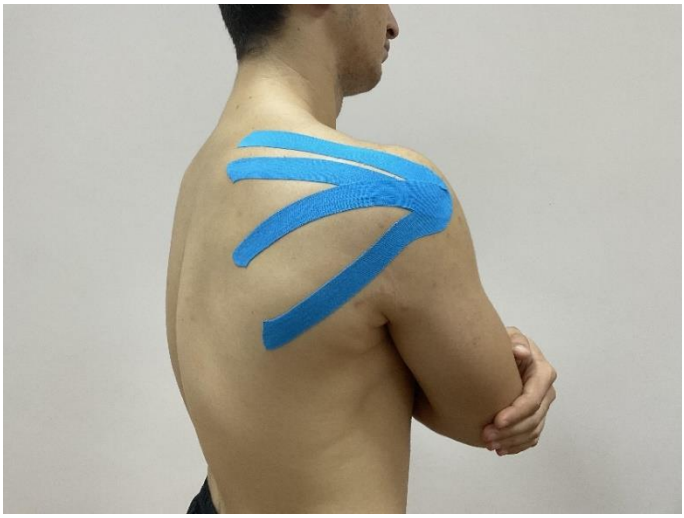


Figure 8. Clinical taping for infraspinatus muscle

Clinical taping application of deltoid muscle

Taping of this muscle occurs in three stages. Tape shape length: In clinical taping of this muscle, a 5 cm I-shaped strip tape is used on all three parts of the deltoid muscle.

First stage (deltoid muscle acromial part taping)

Positioning: The patient's shoulder is in retraction.

Intervention technique: Starting from the acromioclavicular joint, following the deltoid midpart, it is taped without stretching to the deltoid tuberosity.

Second stage (deltoid muscle clavicular part)

Positioning: The patient's arm is in slight extension and external rotation.

Intervention technique: Taping is started from the outer part of the clavicle 1/3, following the anterior part of the deltoid muscle and adhered to the deltoid tuberosity without stretching.

Third stage (deltoid muscle spinal part):

Positioning: The patient's arm is in slight flexion and internal rotation.

Intervention technique: Taping is started from the posterior-outer part of the spine of scapula, followed by the posterior part of the deltoid muscle and adhered to the deltoid tuberosity without tension (Figure 9).

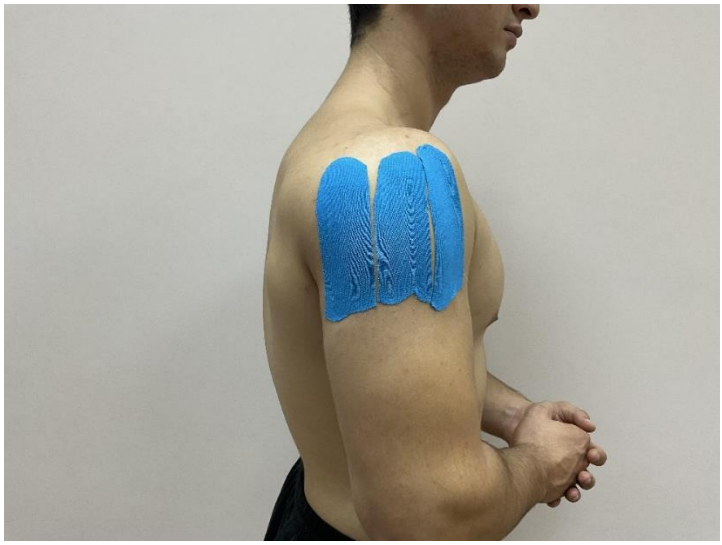


Figure 9. Clinical taping for deltoid muscle

Clinical taping application of teres minor muscle

Tape shape and length: In the clinical taping of the infraspinatus muscle, a 5 cm Y-shaped tape is applied with the inhibition technique.

Positioning: The patient's shoulder is positioned in protraction, mild abduction, horizontal flexion, and internal rotation.

Intervention technique: While the base of the Y-shaped tape is adhered to the lowest part of the greater tubercle by 25% stretching, the upper arm of the Y-shaped tape is attached to the medial edge of the scapula by following the spine of scapula without stretching, and the lower arm is tightened by 15% stretching the teres minor muscle. It is adhered to the lower corner of the scapula by following it (Figure 10) (Snodgrass et al., 2018).

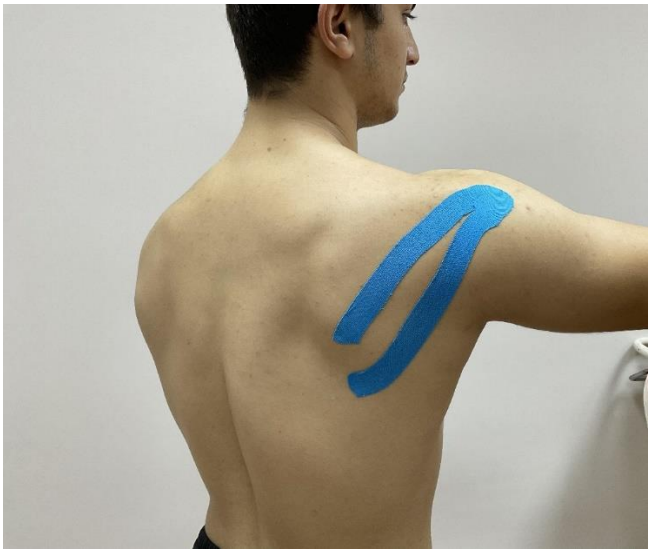


Figure 10. Clinical taping for teres minor muscle

Clinical taping application of subscapular muscle

Tape shape and length: In the clinical taping of the subscapular muscle, a 5 cm Y-shaped tape is applied with the inhibition technique.

Positioning: The patient's arm is positioned in 45° of abduction, 90° of flexion and internal rotation.

Intervention technique: Lesser tubercle is palpated. The initial part of the Y-shaped tape is adhered to the lesser tubercle without stretching, the upper arm following the lower part of the spina, and the lower arm following the lateral edge of the scapula (Figure 11) (Smith et al., 2021).

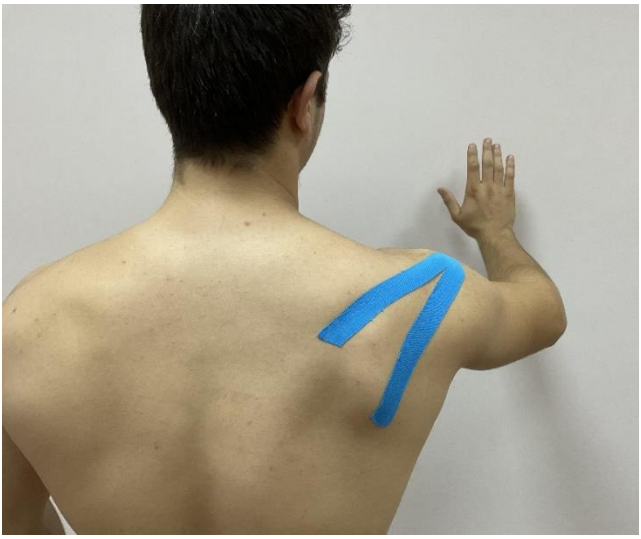


Figure 11. Clinical taping application of subscapular muscle

Clinical taping application of biceps brachii muscle

Tape shape and length: In the clinical taping of the biceps brachii muscle, a 5 cm X-shaped tape is applied with the inhibition technique.

Positioning: The patient's arm is positioned in abduction and external rotation.

Intervention technique: The initial part of the first tape is adhered to three fingers under the tuberosity of radius by 50% stretching and following the long head of the biceps brachii muscle, it is adhered to the supraglenoid tubercle without stretching. The second tape is adhered three fingers under the medial epicondyle by 50% stretching and crossed the first tape and followed the short head of the biceps brachii muscle to the coracoid process (Figure 12) (Snodgrass et al., 2018).

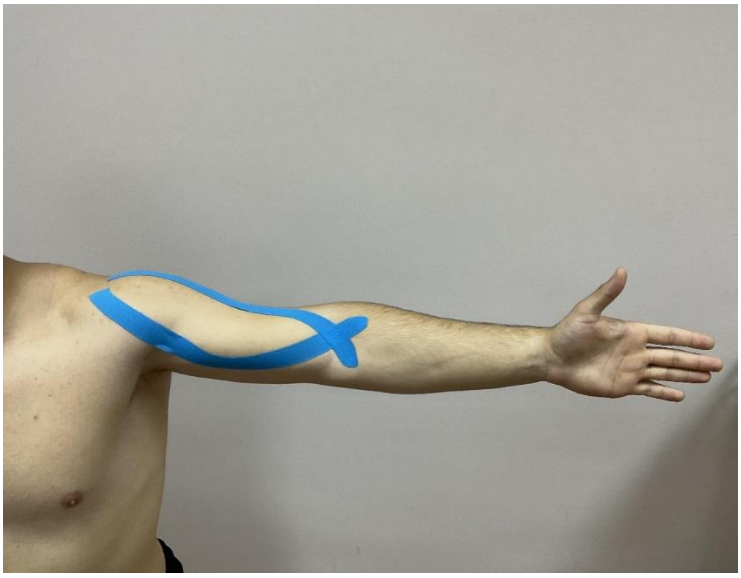


Figure 12. Clinical taping for biceps brachii muscle

Clinical taping application of thoracic outlet syndrome

Three different techniques are used for thoracic outlet syndrome clinical taping.

Muscle inhibition technique is applied to reduce tension. Two Y-shapes, one X-shape and one I-shape tape are preferred for this application. Implementation takes place in four steps.

1-The beginning part of the I-shape tape is adhered to the acromioclavicular joint level with slight tension, followed by the subclavius, and adhered to the sternoclavicular joint level without stretching.

2- The base of the Y-shaped strip tape is adhered to the coracoid process without stretching. The Y-shape tape is adhered by light stretching, following the upper part of the pectoralis minor muscle, and the lower arm of the tape following the lower part of the pectoralis minor muscle.

3- The X-shaped tape is attached in the same way as the biceps brachii muscle technique.

4- The second Y-shape tape is used to relax the scalenus anterior. The patient's head is positioned in lateral flexion towards the contralateral shoulder. The base of the Y-shaped tape is adhered 7 cm lateral to the

sternum at the level of the first rib. The upper arm of the Y-shaped strip tape is adhered to the C3 and lower arm of the C6 transverse process with very slight stretching (Figure 13) (Aygül Ortaç, Sarpel, & Coşkun Benlidayı, 2020)

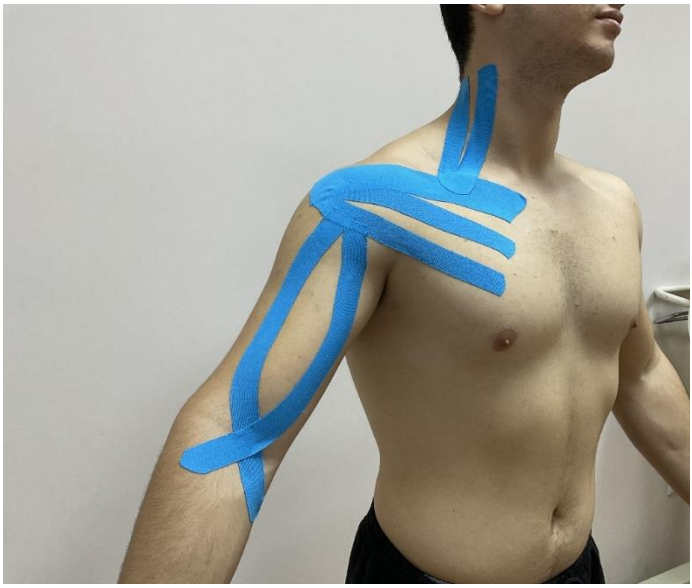


Figure 13. Clinical taping for thoracic outlet syndrome

REFERENCES

Aygül Ortaç, E., Sarpel, T., & Coşkun Benlidayı, İ. (2020). Effects of kinesio taping on pain, paresthesia, functional status, and overall health status in patients with symptomatic thoracic outlet syndrome: A single-blind, randomized, placebo-controlled study. *Acta Orthopaedica et Traumatologica Turcica*, *54*(4), 394–401. https://doi.org/10.5152/j.aott.2020.19042

Bakhsh, W., & Nicandri, G. (2018). *Anatomy and Physical Examination of the Shoulder*. Retrieved from www.sportsmedarthro.com

CLINICAL KINESIOLOGY and ANATOMY. (n.d.).

de Oliveira, F. C. L., de Fontenay, B. P., Bouyer, L. J., Desmeules, F., & Roy, J. S. (2017). Effects of kinesiotaping added to a rehabilitation programme for patients with rotator cuff tendinopathy: Protocol for a single-blind, randomised controlled trial addressing symptoms, functional limitations and underlying deficits. *BMJ Open*, *7*(9). https://doi.org/10.1136/bmjopen-2017-017951

Flores, D. v., Goes, P. K., Gómez, C. M., Umpire, D. F., & Pathria, M. N. (2020). Imaging of the acromioclavicular joint: Anatomy, function, pathologic features, and treatment. *Radiographics*, *40*(5), 1355–1382. https://doi.org/10.1148/rg.2020200039

Huegel, J., Williams, A. A., & Soslowsky, L. J. (2015). Rotator Cuff Biology and Biomechanics: A Review of Normal and Pathological Conditions. *Current Rheumatology Reports*, *17*(1). https://doi.org/10.1007/s11926-014-0476-x

Hughes, P. C., Green, R. A., & Taylor, N. F. (2014). Isolation of infraspinatus in clinical test positions. *Journal of Science and Medicine in Sport*, *17*(3), 256–260. https://doi.org/10.1016/j.jsams.2013.05.011

Iwata, E., Shigematsu, H., Inoue, K., Egawa, T., Sakamoto, Y., & Tanaka, Y. (2017). Muscle Weakness in the Empty and Full Can Tests Cannot Differentiate Rotator Cuff Tear from Cervical Spondylotic Amyotrophy: Pain Provocation is a Useful Finding. *The Open Orthopaedics Journal*, *11*(1), 1081–1086. https://doi.org/10.2174/1874325001711011081

Jain, N. B., Luz, J., Higgins, L. D., Dong, Y., Warner, J. J. P., Matzkin, E., & Katz, J. N. (2017). The Diagnostic Accuracy of Special Tests for Rotator Cuff Tear: The ROW Cohort Study. *American Journal of Physical Medicine and Rehabilitation*, *96*(3), 176–183. Lippincott Williams and Wilkins. https://doi.org/10.1097/PHM.0000000000000566

Ladd, L. M., Crews, M., & Maertz, N. A. (2021, October 1). Glenohumeral Joint Instability: A Review of Anatomy, Clinical Presentation, and Imaging. *Clinics in Sports Medicine*, Vol. 40, pp. 585–599. W.B. Saunders. https://doi.org/10.1016/j.csm.2021.05.001

Lugo, R., Kung, P., & Ma, C. B. (2008). Shoulder biomechanics. *European Journal of Radiology*, *68*(1), 16–24. https://doi.org/10.1016/j.ejrad.2008.02.051

Micheroli, R., Kyburz, D., Ciurea, A., Dubs, B., Toniolo, M., Bisig, S. P., & Tamborrini, G. (2015). Correlation of findings in clinical and high resolution ultrasonography examinations of the painful shoulder. *Journal of Ultrasonography*, *15*(60), 29–44. https://doi.org/10.15557/JoU.2015.0003

Mochizuki, T., Sugaya, H., Uomizu, M., Maeda, K., Matsuki, K., Sekiya, I., … Akita, K. (2008). Humeral insertion of the supraspinatus and infraspinatus. *Journal of Bone and Joint Surgery*, *90*(5), 962–969. https://doi.org/10.2106/JBJS.G.00427

Monaro, P. (n.d.). *Sternoclavicular Joint Injuries*. https://doi.org/10.13140/RG.2.1.1873.9685

Oh, J. H., Park, M. S., & Rhee, S. M. (2018, June 1). Treatment strategy for irreparable rotator cuff tears. *CiOS Clinics in Orthopedic Surgery*, Vol. 10, pp. 119–134. Korean Orthopaedic Association. https://doi.org/10.4055/cios.2018.10.2.119

Şenbursa, G., & Atay, Ö. A. (2011). The effectiveness of manual therapy in Supraspinatus Tendinopathy. *Acta Orthopaedica et Traumatologica Turcica*, *45*(3), 162–167. https://doi.org/10.3944/AOTT.2011.2385

Smith, N., Hotze, R., & Tate, A. R. (2021). A novel rehabilitation program using neuromuscular electrical stimulation (Nmes) and taping for shoulder pain in swimmers: A protocol and case example. *International Journal of Sports Physical Therapy*, Vol. 16, pp. 579–590. North American Sports Medicine Institute. https://doi.org/10.26603/001c.21234

Snodgrass, S. J., Farrell, S. F., Tsao, H., Osmotherly, P. G., Rivett, D. A., Chipchase, L. S., & Schabrun, S. M. (2018). Shoulder taping and neuromuscular control. *Journal of Athletic Training*, *53*(4), 395–403. https://doi.org/10.4085/1062-6050-68-17

Virk, M. S., & Cole, B. J. (2016, January 1). Proximal Biceps Tendon and Rotator Cuff Tears. *Clinics in Sports Medicine*, Vol. 35, pp. 153–161. W.B. Saunders. https://doi.org/10.1016/j.csm.2015.08.010

Yanase, K., Hasegawa, S., Nakamura, M., Yamauchi, T., Nishishita, S., Araki, K., … Ichihashi, N. (2018). Electrical Stimulation to the Infraspinatus on Hypertrophy and Strength of the Shoulder. *International Journal of Sports Medicine*, *39*(11), 828–834. https://doi.org/10.1055/s-0044-102129

CHAPTER 13

APPROACH TO CHILDHOOD ANEMIA

MD. Seyma UNUVAR GOK[1]

[1] Etlik City Hospital, Ankara, Türkiye. drseymaunuvargok@gmail.com, Orcid ID:0000-0003-3520-5498

I. INTRODUCTION

Anemia is defined as less than two standard deviations in hemoglobin concentration, red blood cell count, or hematocrit count at the mean value for sex and age for the normal population (Table 1).[5] (Lanzkowsky, P. et al ;2021)

Anemia can be a sign of disease or it can be isolated. In the presence of an underlying disease, detection and treatment of the cause is very important. In addition, it should be kept in mind that children with congenital heart disease, arteriovenous pulmonary shunt, chronic respiratory failure or hemoglobinopathies may have laboratory hemoglobin levels within the normal or reference range but may be functionally anemic.[12] (Ünal S. et al. 2011)

Table 1. Mean and Lower Limit of Erythrocyte Parameters by Age (-2SDS)

		Hgb (g/dl)		Htc (%)		Rbc (10^{12}/L)		MCV(fL)		MCH (pg)		MCHC (g/dL)		Retikülosit	
Age		Mean	-2SD	Mean	-2SD	Mean	-2SD	Mean	-2SD	Mean	-2SD	Mean	-2SD	Mean	-2SD
Cord Blood		18,5	14,5	56	45	5,3	4,0	108	95	34	31	33	29	3,2	1,8
1-3 days		18,5	14,5	56	45	5,3	4,0	108	95	34	31	33	29	3,0	1,5
1 week		17,5	13,5	54	42	5,1	3,9	107	88	34	28	33	28	0,5	0,1
2 weeks		16,5	12,5	51	39	4,9	3,6	105	86	34	28	33	28	0,5	0,2
1 month		14	10	43	31	4,2	3,0	104	85	34	28	33	29	0,8	0,4
2 months		11,5	9	35	28	3,8	2,7	96	77	30	26	33	29	1,6	0,9
3-6 months		11,5	9,5	35	29	3,8	3,1	91	74	30	25	33	30	0,7	0,4
6months-2years		12	10,5	36	33	4,5	3,7	78	70	27	23	33	30	1,0	0,2
2-6years		12,5	11,5	37	34	4,6	3,9	81	75	27	24	34	31	1,0	0,2
6-12 years		13,5	11,5	40	35	4,6	4,0	86	77	29	25	34	31	1,0	0,2
12-18 years	F	14	12	41	36	4,6	4,1	90	78	30	25	34	31	1,0	0,2
	M	14,5	13	43	37	4,9	4,5	88	78	30	25	34	31	1,0	0,2

Hgb: Hemoglobin, Hct: Hematocrit, Rbc: Red blood cells, MCV: Mean Erythrocyte Volume, MCHC: Mean Erythrocyte Hemoglobin Concentration

II. Epidemiology

Anemia is a serious global public health problem, particularly affecting young children and pregnant women. The World Health Organization (WHO) estimates that 42% of children under 5 years of age and 40% of pregnant women worldwide are anemic. In our country, it is estimated that 32.6% of children in infants and early childhood age group are anemic.[11] (Powers J.M. et al, 2021)

Malnutrition is the most common cause of anemia. Deficiencies in folate and B12 vitamins, especially iron deficiency, are the main nutritional causes of anemia. In addition, hemoglobinopathies and malaria, tuberculosis, HIV and parasitic diseases are also known main causes.[2](Derneği, T. H. 2019)

III. Etiology and Classification

Anemia is categorized as morphological and physiological.

The Morphological Classification is based on erythrocyte sizes and is presented in Table 2. [6](Lanzkowsky, P. et al ;2021)

Automatic blood count devices are of great importance in morphological classification. MCV is an important parameter in the evaluation and differential diagnosis of a patient presenting with anemia in all centers.

Although it varies according to age, MCV is expected in the range of 70-83 fL in the pediatric age group and in the range of 77-87fL in adolescence.

When the erythrocyte volume is found in this value range, it is considered as normocytic, if it is above it, it is macrocytic, if it is below it, it is considered as microcytic.

Table 2. Classification of Anemias According to Erythrocyte Sizes

Microcytic Anemia	Normocytic Anemia	Macrocytic Anemia
(MCV<70 fL) Iron Deficiency Anemia Thalassemia Syndromes Sideroblastic Anemias Chronic Inflammation Lead Poisoning Severe Malnutrition Unstable Hemoglobinopathies	(MCV 72–79 fL) Congenital Hemolytic Anemias Aplastic Anemia Acute Blood Loss Acute Infection Chronic renal failure Dyserythropoietic Anemias Hypersplenism	(MCV>85 fL) <u>Without Megaloblastic Changes;</u> • Aplastic Anemia • Diamond Blackfan Anemia • Hypothyroidism • Congenital Dyserythropoietic Anemia • Bone Marrow Infiltration • Liver Failure <u>With Megaloblastic Changes;</u> • Vitamin B12 Deficency • Folate Deficency • Hereditary Orotic Aciduria • Wolfram Sendromu

Physiological Anemia Classification is based on etiological foundations (Table 3).[6] (Lanzkowsky, P. et al ;2021)

It may be caused by one or a combination of the following causes;

- Failed or ineffective erythropoiesis (decreased production in the bone marrow)
- Hemolysis (increased destruction in the peripheral or bone marrow)
- Hemorrhage (erythrocyte loss)

Table 3. Classification of Anemias According to Pathophysiological Characteristics in Childhood

1) Ineffective Erythropoiesis *A. Malnutrition* i. Poor/Imbalanced Nutrition [eg excessive cow's milk consumption, vegan etc.] ii. Increasing demand [fast growth etc.] iii. Decreased absorption iv. In its deficiency, suppressing the bone marrow; lack of iron, folate, protein, thyroxine; Deficiency of vitamins C, B12 and B6 *B. Bone marrow insufficiency* I. Aplasia in a single cell line ii. Aplasia in multiple cell lines • Congenital Fanconi anemia, Dyskeratosis Congenita • Acquired iii. Infiltration • Benign (eg. Osteopetrozis, depo hastalıkları) • Primary malign (eg. leukemia, myelofibrosis) • Secondary malign (eg. neuroblastoma, lymphoma) iv. Dyshematopoietic anemias • Anemia of chronic disease • Kidney failure and liver disease • Disseminated malignancy • Connective tissue diseases • Malnutrition • Sideroblastic anemias
2. Blood loss Obvious or occult blood test positive
3. Hemolytic anemia A. Corpuscular I. Membrane defects (spherocytosis, elliptocytosis) ii. Enzymatic defects (pyruvate kinase, G6PD) iii. Hemoglobin defects B. Extracorpuscular • Isoimmune • Autoimmune

IV. Clinical Symptoms

The course of anemia, whether it is acute or chronic, affects its clinical findings. For example, while the findings are more severe in anemia with an acute process, the findings in chronic anemia tend to be milder due to compensatory mechanisms. In mild to moderate anemia, weakness, loss of appetite, pallor may occur. When Hgb<7g/dl, that is, in deep anemia, decrease in effort capacity, pain in the legs, cardiac murmur, tachycardia, easy breakage of hair and nails, spoon nails, slowdown and retardation in neurological functions, pica (nutrition with non-food products), angulerstomatitis, malabsorption, atrophy and susceptibility to infections can be seen in the tongue papillae.[1] (Anak S. et al, 2011)

Another important issue that should not be forgotten is that in cases followed up with iron deficiency, restlessness and a decrease in learning capacity can be observed even without the development of anemia.[1](Anak S. et al,2011)

V. Diagnostic Approach

A detailed history and examination form the basis for the approach of a patient who applied with the complaint and/or findings of anemia. In this way, many examinations are prevented from being performed without indication.

Steps of diagnostic approach to Anemias are presented in Table 4.[9] (Orkin S. et al,2014) The following are the topics to be questioned in the story.

Table 4.1. History in Diagnostic Approach to Anemias

Patient Gender	G6PDH Deficiency is X-linked, more common in males
Family History	Race and family origin should be questioned in erythrocyte enzyme deficiencies and Hereditary Membrane Diseases.
Age at which Application and Symptoms were Detected	Congenital infections and bleeding in the neonatal period; Milk, Play and insufficient/unbalanced nutrition in school children and adolescents are the most common causes. Menstrual bleeding is common in adolescent girls.

Nutritional Characteristics	The history of breastmilk intake, iron supplementation, the age and amount of starting cow's milk, the month of starting complementary food and its content should be questioned.
Drug Use	Antiepileptic, antihypertensive drugs and chemotherapeutic use should be questioned. In addition, enzyme deficiencies should be considered in hemolytic anemia that develops with oxidants such as aspirin.
Chronic Disease	Inflammatory diseases such as SLE and Lupus can also lead to thyroid gland disorders
Infection	Viral diseases, parasitic infestations such as malaria and especially intracellular bacteria infections
Other	Jaundice, gastrointestinal symptoms, perinatal history

Anemia is based on different causes in each age group. Anemia caused by congenital causes is noisy due to its acute findings and is diagnosed quickly. However, in cases where anemia findings become chronic, diagnosis may be difficult due to homeostatic balance. [1] (Anak S. et al, 2011)

It should also be kept in mind that the diagnosis of FanconiAplastic Anemia, which is expected to be diagnosed in the early period, can be made between the ages of 4-6 years because its laboratory and clinical findings appear late, and because hemoglobin F is dominant in the natal period, patients with beta thalassemias present symptoms after 6 months of birth.[3](Fettah A. et al,2021)

Physical examination is important and guiding in the presence of an underlying disease as well as detecting the signs of anemia. An idea of the acute or chronic development of anemia can be obtained even by physical examination alone. A patient with signs of heart failure such as jugulovenous fullness, crepitanrals, pretibial edema has an acute condition that requires urgent intervention. On the other hand, if growth and development retardation is also detected in a child or adolescent who is in rapid growth period, it indicates the presence of chronic anemia. [1] (Anak S., et al , 2011)

Table 4.2. Physical Examination in Diagnostic Approach to Anemias

Vital Findings	Every patient presenting with anemia should be evaluated for signs of failure.
Skin - Jaundice - Petechiae, Purpura, Hemangioma - Ulcer in Lower Extremity - Painless Glossitis, Angular Stomatitis	
Lymphadenopathy/Splenomegaly	It should be evaluated for infective agents such as tuberculosis, HIV, infectious mononucleosis or lymphoproliferative disease and leukemia, especially if it is widespread and pathological.
Face - Zygomatic and Maxillary Bone Dislocation - Microcornea - Yellow/Blue Colored Sclera	
Shield Chest	Diamond Blackfan Anomaly
Unilateral Absence of Pectoral Muscle	Poland Syndrome

In cases followed up with chronic hemolytic anemia, 'Hemolytic Face' is diagnostic. Dislocation of the parietal and frontal bones, irregularity in the maxillary teeth and flattening of the nasal root are phenotypic changes. [8] (Lanzkowsky, P. et al ;2021)

The blue appearance of the sclera can be seen in both iron deficiency and osteopetrosis.

In malignancies infiltrating the bone marrow and aplastic anemia, findings such as petechiae and purpura may be detected on the skin. Kasabach-Merrit Syndrome should be considered in accompanying especially large cavernous hemangiomas.

Finally, in FanconiAplastic Anemia, diffuse hyperpigmentation and skeletal anomalies accompanying anemia are detected. Microcephaly, thumb and radius anomalies are expected.

Today, although it has many detailed laboratory facilities, hemogram, peripheral smear and reticulocyte evaluation still form the basis of diagnosis in every step center in the diagnosis and treatment of anemia. Hemoglobin,

hematocrit indices, white blood cell and platelet counts are possible with the hemogram device available in all centers. With peripheral smear, leukocyte formula and platelets, as well as erythrocyte size and morphology are evaluated in detail.[4] (Hermiston, M. et al, 2002)

In the preliminary diagnosis of anemia, laboratory data should be evaluated according to age and gender. In each case in which anemia is detected, other series should also be evaluated to exclude the presence of an underlying disease, especially infiltrating the bone marrow.

Although bone marrow aspiration is not recommended for routine diagnostic use, it is included in the algorithm when a symptom of bone marrow involvement or infiltration is encountered.

Reticulocyte count is important in the diagnosis and differential diagnosis of anemia. In a healthy person, reticulocyte in the peripheral blood is in the range of 0.5-1%.[3] (Fettah A. et al,2021)

Reticulocytosis in anemia due to hemolysis and hemorrhage; Reticulocytopenia is seen in anemia due to production defects. In deep anemias, the reticulocyte ratio should be interpreted by correcting for decreased hematocrit; thus, the 'Corred Reticulocyte Count' is determined.[3] (Fettah A. et al,2021)

$$\text{'Corrected Reticulocyte Count'} = \text{Reticulocyte} \times \{\text{Hematocrite}\}$$

Although iron deficiency is the most common cause of anemia in childhood, detailed investigations may be required to investigate the underlying causes. [6] (Lanzkowsky, P. et al ;2021)

Table 4.3. Laboratory in Diagnostic Approach to Anemias

In Every Patient Followed Up with Anemia • Hemoglobin, Hematocrit • RBC, MCV, RDW • Leukocyte Count • Platelet Count • Peripheral Blood Smear • Reticulocyte Count
In the Patient Followed Up with Hemolytic Anemia

• Serum Haptoglobin, Bilirubin and Urine Urobilinogen • Corpuscular; Osmotic Fragility, Hemoglobin Electrophoresis, Kleihauer-Betke Test, Enzyme Levels • Extra Corpuscular; Antiglobulin Test, Donath-Landsteiner Antibodies, Anti-Nuclear Antibodies
In the Patient Followed Up with Aplastic Anemia • Bone X-rays • Evaluation of bone marrow aspiration • Genetics Department Consultation
In the Patient Followed Up with Iron Deficiency Anemia (IDA) • Serum iron, iron binding capacity • Transferrin Saturation Index • Serum ferritin level • Stool for occult blood • Gastroenterology Department Consultation in treatment-resistant patients
In the Patient Followed Up with Vitamin B12 and Folic Acid Deficiency • Serum Vitamin B12 and Folic Acid Level • Schilling Test and Gastric Analysis in treatment-resistant cases
Other; Rheumatological examinations, viral agents that suppress the bone marrow can be examined according to the patient's clinic.

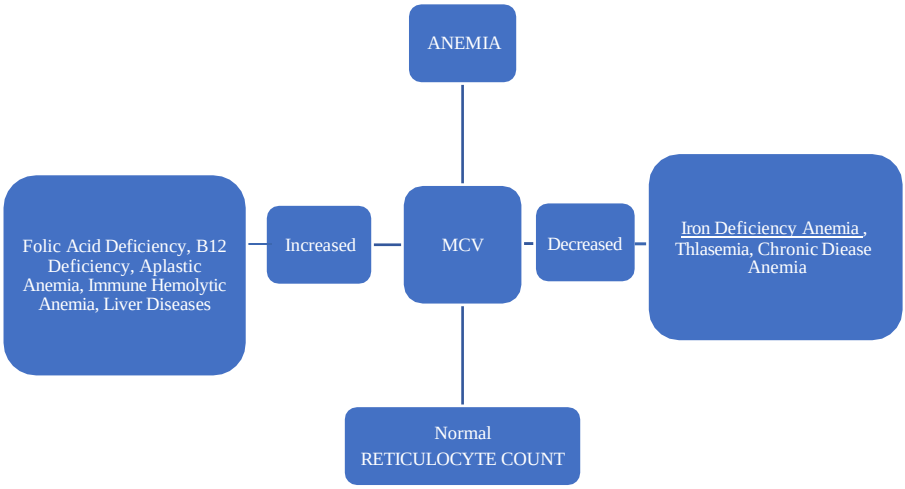
VI. Differential Diagnosis

Anemia, which develops on the basis of infection, is a frequent reason for referral, especially in pediatric clinics. Chronic inflammatory processes can lead to anemia. In acute infection periods, the Hgb value may decrease by 1-1.5 g/dl in a week.

When the patient is examined during this period, hemoglobin and serum iron are found to be low in anemia developing secondary to both IDA and infection. In the differential diagnosis, MCV and ferritin are found to be low in IDA. Ferritin, an acute phase reactant, is found to be normal or elevated in anemia secondary to infection. MCV is normocytic. While RDW is increased in IDA, it is normal in infection-related anemia. [7] (Lanzkowsky, P. et al ;2021)

Laboratory data should be evaluated according to age and gender in a pediatric patient presenting with anemia. After a detailed history and physical examination, the differential diagnosis can be made with an algorithm based on the morphological approach after the first step examinations are completed (Table 5). [6](Lanzkowsky, P. et al ;2021)

Table 5.1. Differential Diagnosis in Childhood Anemias



Microcytic anemia in children is most commonly caused by iron deficiency.[2] (Derneği, T. H. (2019).) Thalassemia is also a common cause of microcytic anemia and its differential diagnosis is important in clinical practice.8 (Lanzkowsky, P. et al ;2021) Otherwise, it is possible to encounter children who constantly use iron preparations. Peripheral smear shows microcytosis, anisocytosis, target cells and poikilocytosis in IDA. IDA is diagnosed with low serum iron and ferritin and increased free iron binding capacity.

When normal globulin chains (α2β2) in a healthy hemoglobin structure are mutated, thalassemia with hemolytic anemia occurs and clinically correlates with the severity of the mutation.[8] (Lanzkowsky, P. et al ;2021)

Thalassemia carriers have a mild anemia. The Mentzer Index, which is frequently used in the differential diagnosis of IDA and thalassemia, is determined by dividing MCV by RBC. Mentzer Index <13 is in favor of thalassemia, and >13 is in favor of IDA.[12] (Unal S. et al.,2011) Hemoglobin electrophoresis should be requested for definitive differential diagnosis in thalassemia and IDA.[6](Lanzkowsky, P. et al ;2021) However, in anemia with deep iron deficiency, Hgb A_2 may be falsely low in electrophoresis. For this reason, it is important to treat iron deficiency first and to request the test in patient follow-up.[3] (Fettah A., et al , 2021)

Table 5.1.1 Differential Diagnosis in Patients with Hypochromic Microcytic Anemia

		Thalassemia Carrier		
	Iron Deficiency Anemia	Beta	Alfa	Chronical Desease
Hemoglobin(g/dL)	3-10	9-11	10-12	8-11
Serum iron	Low	High /Normal	Normal/ High	Low
Ferritin	Low	High /Normal	Normal/ High	Low / High
TIBC	High	Low /Normal	Normal	Low
Transferrin Saturation	Low	High	Normal/High	Low
Hgb A_2	Low/Normal	High	Normal	Normal
Sideroblast in Bone marrow	Decreased	Normal	Normal	Decreased

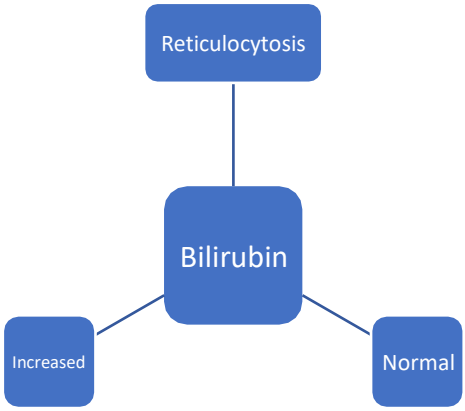
Genetic counseling should be given to all patients with thalassemia carriers.

Macrocytic anemia is less common in childhood. The most common cause of megaloblastic anemia in children is vitamin B12 deficiency. Peripheral smear shows hypersegmented neutrophils and macroovalocyte. Macrocytic anemia without megaloblastic changes can be seen in childhood in Diamond

Blackfan Anemia, MDS, hypothyroidism, and liver diseases.[10] Rudolph A., et al, 2003)

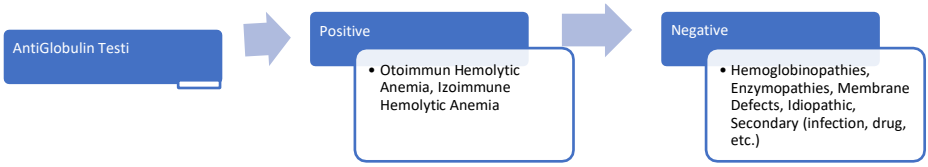
Algorithm continues with reticulocyte counting in normocytic anemia.[6] (Lanzkowsky, P. et al ;2021)

Table 5.2.1. Differential Diagnosis in Normocytic Anemia



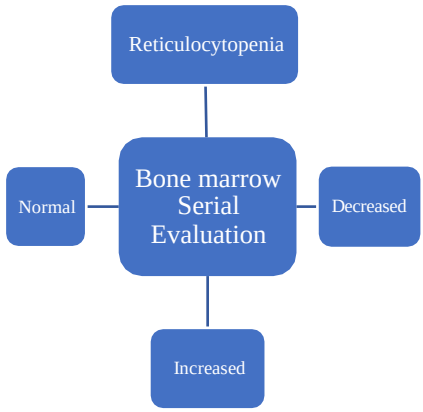
Hemolytic anemia or bleeding is encountered in normocytic anemia associated with reticulocytosis. In cases with normal bilirubin levels, the cause is bleeding. When the bilirubin level is found to be high, the patient should be examined for hemolytic anemia. Direct Antiglobulin Test (DAT) should be done.

DAT positive detection extra corpuscular; Detection of DAT negative leads to the causes of corpuscular hemolytic anemia.



In normocytic anemia associated with reticulocytopenia, the etiological factors affecting the bone marrow should be investigated and other blood series should be evaluated first.[6] (Lanzkowsky, P. et al.;2021)

Table 5.2.2. Differential Diagnosis in Normocytic Anemias



If white blood cell (WBC) and platelet (plt) values are increased, infectious causes; If it is decreased, the patient should be examined for aplastic anemia and malignancies. If these series are found in normal values, the prediagnoses should be Pure Erythroid Aplasia, DiamondBlackfan Anomaly, TEC (transient erythroblastopenia of childhood).

REFERENCES

1. Anak S.,Özbek N.,Avcı Z., Turkish Pediatric Hematology Society, Pediatric Hematology, 2011 , Erythrocyte Diseases, Diagnostic Approach to Anemias,Istanbul Tıp Kitabevi chapter V ; 173-345
2. Derneği, T. H. (2019). Çocuklarda Demir Eksikliği Anemisi Tanı ve Tedavi Kılavuzu. *Ulusal Tedavi Klavuzu*,
3. Fettah A.,Yaralı N.,2021 MD.Sami Ulus Textbook of Pediatrics, Chapter 16, Approach to the child with anemia, 920-932
4. Hermiston, M. L., & Mentzer, W. C. (2002). A practical approach to the evaluation of the anemic child. *Pediatric Clinics*, *49*(5), 877-891.
5. Lanzkowsky, P., Lipton, J., & Fish, J. D. (2021). *Lanzkowsky's manual of pediatric hematology and oncology 7th edition*. Elsevier. Hematological reference values 797-781
6. Lanzkowsky, P., Lipton, J., & Fish, J. D. (2021). *Lanzkowsky's manual of pediatric hematology and oncology 7th edition*. Elsevier. Chapter 3 37-61
7. Lanzkowsky, P., Lipton, J., & Fish, J. D. (2021). *Lanzkowsky's manual of pediatric hematology and oncology 7th edition*. Elsevier. Chapter 4 61-80
8. Lanzkowsky, P., Lipton, J., & Fish, J. D. (2021). *Lanzkowsky's manual of pediatric hematology and oncology 7th edition*. Elsevier. Chapter 9 161-191
9. Orkin, S. H., Nathan, D. G., Ginsburg, D., Look, A. T., Fisher, D. E., & Lux,
10. S. (2014). *Nathan and Oski's hematology and oncology of infancy and childhood*. Elsevier Health Sciences. 52-75
11. Rudolph, A. M., Kamei, K. R., Overby, J. K., & Yurdakök, M. Rudolph¨ s Fundamentals of Pediatrics 2003. *Öncü Basımevi, Ankara. 513-545*
12. Powers, J. M., Sandoval, C., & Lorin, M. I. (2021). Approach to the child with anemia.
13. Ünal, S., Balcı, Y. I., & Toprak, S. K. (2011). Eritrosit hastalıkları ve hemoglobin bozuklukları tanı ve tedavi kılavuzu. *Bölüm III Yetişkinde Demir Eksikliği Tanı ve Tedavi Kılavuzu Ankara: Türk Hematoloji Derneği*, 23-33.

BÖLÜM 14

THE ROLE OF THE CENTRAL NERVOUS SYSTEM IN SEXUAL PROCESSES

Dr. Öğrt. Üyesi Tuba GÜL[1]

[1] Ordu Üniversitesi, Tıp Fakültesi, Nöroloji Anabilim Dalı, Ordu, Türkiye. tglyzc@hotmail.com, Orcid ID: 0000-0001-6003-5975

ENTRANCE

The normality of male sexual behavior depends on the healthy functioning of the hypothalamic-pituitary-testicular axis, peripheral and central nervous system. Treatments that alter the concentration of sex hormones in the bloodstream or any disorder in the nervous system can affect sexual behavior, reproductive activity, and many other organ systems. The time it takes for hormones to act on the target organ by passing into the bloodstream is longer than the effect that occurs by the neural route. For example: Sexual behavior in male rats begins to decrease about 1 week after castration and does not disappear until 3 weeks after castration. However, it has been reported that the pattern of sexual behavior changes in about 1 hour with the increase in the concentration of circulating testosterone (T) under the influence of neuroendocrine mechanisms. Therefore, in the evaluation of the mechanisms that control sexual behavior, the most accurate interpretation of the results may be possible by elucidating whether the process is directly due to a hormonal effect or changes in neuronal conduction mechanisms (Yardımcı, 2015)

Sexual activation cycle: It is a known fact that the central nervous system is through the hypothalamus, brain stem, spinal cord, autonomic system, reflex pathways, and synaptic transmissions. Sexual desire, sexual functional functioning, and all processes related to it are affected by any changes or pathologies in these pathways (Georgiadis, 2015).

Although the sexual behavior of rodents is not the same as that seen in humans, since neurotransmitters, brain structures, neuronal networks, and the motivational and complementary aspects of sexual behavior are fundamentally similar, rodent models are often used in research to elucidate the complex pathogenesis of neurological, cardiovascular, and metabolic diseases in humans, especially in the representative of the male gender. In this regard, the most suitable rodent group in terms of being a model of sexual behavior in rats. (Bialy, et al., 2019).

This study, which was prepared based on a detailed literature review and multifaceted examinations and based on scientific evidence and clinically supportive data, is a compilatory review in which sexual functions and reproductive system are discussed in terms of neuroanatomical, neuroendocrinological, and neurophysiological aspects, especially in terms of the male gender.

Of The Sexual Cycle In Men

In the process of sexual behavior in men, the return of physiological changes in the genital organs to the pre-stimulation state after the ejaculation stage is considered as the "dissolution phase". After this stage, there is a stage of non-response that must pass through the routine functioning of neuroendocrine and neurophysiological mechanisms in order to be sexually stimulated again. Depending on many factors such as the presence of diseases affecting the systems that control sexual functions and the effect of the aging process, the duration of this stage varies from individual to individual (Şirin and Kendirci, 2016).

The Glans penis is a primary erogenic area and is involved in both the initiation of an erection and the last stage of ejaculation, the expulsion and orgasm phase. The sensation of the skin of the penis, also called nociceptor, with a thin myelin sheath, is common in the glans tissue, but is taken by the n. dorsalis penis, which is found in the densest corona and frenulum, and is transferred to the medulla spinalis through n. pudendus (Çelik, et al., 2017).

When sequential and cumulative impulses exceed a certain level, there is a discharge of neural conduction in bodies that perceive pressure, superficial, touch, and deep sensation under the skin. This last stage, in which the penis turns into a flaccid state as a result of the effects on the vascular and smooth muscle with the activation of the thoracolumbar sympathetic pathway, is called the detumescent phase. Since the penile sense, that is, the function of sexual activation begins to form neurodegeneration in peripheral neurons with age, it gradually decreases and may disappear close to the fullest, if there are risk factors such as underlying diabetes. (Aykan, et al., 2017).

In addition, anti-inflammatory and antinociceptive agents cause a delay in both sensing sensory inputs and in the ejaculation response secondary to sequential stimulation, as they reduce and prevent peripheral sensitivity (Atan and Tuncel, 2013).

Neuroanatomıc Areas That Control Sexual Behavıor

The main neuroanatomic areas that control sexual behavior are; The anterior medial brain bundle includes the anterior region of the medial preoptic area (MPOA) of the hypothalamus and related limbic-hippocampal structures and the ventral tegmentum of the midbrain (Boyarsky and Hirschfeld, 2000). It

has been shown that different results occur depending on the stimulation of various areas of the hypothalamus. In animal experiments, it has been observed that as a result of the stimulation of the ventromedial (VMH) nucleus of the hypothalamus by electricity, the animals calm down and drain the animal's sperm (ejaculation), while sexual power is lost in damage (Üngüren, 2000).

The ventrolateral (VLH) subdivision of VMH in rats contains neurons whose activity increases during male-male and male-female social encounters. Research has shown that activation of estrogen (E2) receptors in this region promotes assembly behavior, sniffing and convergence movements in both male and female subjects. (Lee, et al. 2014)

MPOA at the rostral end of the hypothalamus is crucial for the regulation of both sexual arousal and performance stages of male sexual behavior. There are evident studies showing that male sexual behavior is impaired following MPOA lesions and increases with MPOA stimulation (Shimura, et al., 1994).

The main source of innervation of MPOA is the medial amygdala (MeA). Chemical stimulation of MeA in anesthetized male rats increases dopamine (DA) levels in extracellular MPOA and facilitates male sexual behavior (Dominguez and Hull, 2001).

In one of the studies demonstrating that the estrogen receptor alpha (ERα) is a critical part of regulatory processes related to normal reproduction and sexual behavior, ERα-disabled male and female mice were divided into groups and 0.2% ascorbic acid and DA were administered. Mating behavior towards females continued in male mice that underwent DA but sexual functions were blocked in the ascorbic acid group. This has shown that there is another way besides ERα for masculine sexual behavior to occur in mice, which is controlled by the DA (Wersinger and Rissman, 2009). The VLH subdivision of VMH in rats includes neurons whose activity increases during male-male and male-female social encounters. Research has shown that activation of E2 receptors in this region encourages assembly behavior, socio-sexual behaviors, sniffing, intimacy, and mate preference movements in both male and female subjects (Lee, et al., 2014).

The Role Of The Autonomous Nervous System In Sexual Behavıor

The receptors found in tissues that are inflamed by the parasympathetic system (PS) are known as "muscarinic receptors (M)". The stimulation that comes with the nerve axon is transmitted to the M receptors in the target organ with the release of acetylcholine from the presynaptic nerve end, and the effect of the stimulation varies according to the subtype of the receptor. There are five subtypes of M receptors; M1: It is located in the cerebral cortex, hippocampus, stomach M2: It is located in the heart, nervous tissue and smooth muscle and has the functions of opening the autoreceptor, cAMP reducing, K channels, M3: Glands, smooth muscles and endothelium, external glands gastrointestinal tract, respiratory system, brain, M4: Neostriatum, M5: Substantia nigra, striatum, hippocampus Pons, medulla, cerebellum (Turkmen and Akçay, 2009).

PS is involved in both erection and ejaculation formation. With the exception of the striated muscle and the vessels leading to the erectile organs, the parasympathetic fiber does not reach the vascular system. Here, the task of the mediator neurotransmitter acetylcholine is to create vasodilation through muscarinic receptors in arteries and veins (Turkmen and Akçay, 2009). With PS stimulation in the process of erection; With dilatation of the penile arteries, blood flow into the lacunar area increases, and intracavernous pressure rises. Following arterial dilatation, the trabecular smooth muscle relaxes, thereby increasing the lacunar area complicity and concentrating blood there (Kizilkan, 2020)

The second phase in the formation of escalation, the emulsion phase, is in the PSkontol. At this stage, the semen is expelled with rhythmic contractions of the bulbocavernous and ischiocavernous muscles, the closure of the bladder neck and the relaxation of the external urethral sphincter (Şirin and Kendirci, 2016). Atropin is an alkaloid derived from the plant called Atropa belladonna (Belladonna) and is the prototype of muscarinic receptor antagonists. It has both central and peripheral efficacy and has a dose-dependent effect on all M receptors (Cabadak, 2006).

HORMONAL EFFECT

According to Stahl, neurotransmitters contribute to the formation of the process by acting on three phases in the human sexual response cycle. In the

stage of sexual desire, which is the first stage; DA, melanocortin, T and E2 have a positive effect, while prolactin and serotonin (5HT) have a negative effect. The second stage, arousal, is associated with erection in men and genital wetting and lubrication in women, and various neurotransmitters including nitric oxide (NO), norepinephrine (NE), melanocortin, T, E2, acetylcholine (Ach), and DA have been shown to facilitate sexual arousal. In men, DA and NO have weak positive effects, 5HT inhibitors, and NE facilitating effects on the third stage of peripheral ejaculation and central orgasm (Stahl, 2008).

5-Hydroxytryptophan

5-Hydroxytryptophan (5-HTP) is an intermediate substance naturally composed of tryptophan and acts as a precursor molecule in the synthesis of 5HT. (Maffei, 2021). One study examined how low and high doses affected sexual functions by administering different molecules in male rats. Given in low doses, thioridazine (first-generation antipsychotic) and chloriepipramine (tricyclic antidepressant); It has been shown to prolong ejaculatory delay (EL) and increase the number of bonds (ML), but does not change the number of intromissions (IL) before ejaculation. Phentolamine (peripheral noradrenaline inhibitor) and phenoxybenzamine (central NA inhibitor); increased doses led to the suppression of all aspects of sexual behavior. 5-HTP and benserazide (inhibitor of the enzyme decarboxylase in the conversion of 5-HTP-sarotonin); chlorimipramine and thioridazine. Zimelin or Alaproclate (selective serotonin reuptake inhibitor (SSRI)); did not affect mating behavior. Administration of these drugs in higher doses; caused some animals to be unable to initiate sexual activity, prolonging the post-ejaculation interval (PEI) in all subjects, but ejaculation latency (EL) remained unchanged. Ultimately; It was concluded that the prolonged ejaculation delays observed following treatment with thioridazine or chlorimipramine were not due to blockade of central or peripheral adrenergic alpha receptors (Ahlenius, 1979).

Serotonin (5-hydroxytryptamine) is a hormone produced by neuroendocrine cells located mainly in the small intestine and large bronchi, in addition to being an important neurotransmitter in the CNS. In several studies on 5HT and male sexual activity, it has been reported that increased 5HT levels have an inhibitory effect on sexual motivation, ejaculation, and orgasm. In male rats, EL is shortened and EF is increased due to a decrease in 5HT levels. So,

we can say that the decrease in serotonergic activity facilitates the sexual behavior of male rats. There are publications that 5-HT released after ejaculation was involved in the formation of the silent period in the PEI period. In a large-scale study, 5-HT release increased in the anterior lateral hypothalamic area of male rats after ejaculation, there was no change in the process before ejaculation, and during a subsequent mating series, levels decreased towards basal values, and after microinjection of Alaproklate, a selective 5HT reuptake inhibitor, into this area; ML, IL and EL durations have been shown to increase and inhibit mating. In MPOA, extracellular 5-HT release remained constant throughout mating, and alaproclate microinjection into this area did not significantly alter sexual behavior. These data suggest that serotonergic inhibition occurs through MPOA, not through the lateral hypothalamus (Lorrain, et al., 1997).

Oxytocın

Oxytocin (OT) is a highly important hormone known to function in many different situations, such as pregnancy, breastfeeding, commitment, autism and severe anxiety, disordered social behavior, and to promote social and reproductive behaviors in mammals. A study; It has been shown that OT microinjected into MPOA, an important integrative site for male sexual behavior, facilitates mating in sexually experienced and naïve male rats, but intra-MPOA injection of an OT antagonist (OTA) inhibits mating. In another study; sexually experienced men had higher levels of OT receptor (OTR) protein in MPOA than sexually naïve men and those with first-time sexual activation. Results; It has shown that OT in MPOA facilitates mating in both sexually naïve and experienced males, that some of the behavioral effects of OT are mediated by OTR, and that sexual experience is associated with increased OTR expression in MPOA (Gil, et al., 2013).

Gonadotropın-Secretıng Hormone

The half-life of FSH caused by the stimulating effect of gonadotropin-releasing hormone (GnRH) from the anterior lobe of the pituitary is 1-3 hours. While the important effect of FSH on the testicles is to stimulate spermatogenesis and Sertoli cells, the importance of LH in terms of the male reproductive system is to stimulate the release of T by acting on the Leydig cells in the testicles. Small changes in the GnRH level have no apparent effect

on FSH release. In response to long-term stimuli in GnRH, FSH responds only after a few hours. The release of LH as a result of transmissions from GnRH to the anterior pituitary gonadotrophs is in a pulsatile manner unlike FSH and may vary blindly with instantaneous changes in GnRH (Demir, 2019).

Less LH secretion in the brain results in less T production and impaired sperm production. Many causes such as advancing age, testicles, and pituitary/hypothalamic defects can cause decreased LH and GnRH secretion and consequently decreased T production in the testicles. It has been shown by many studies that a decrease in T levels in humans causes physical changes such as decreased libido, emotional changes such as sleep disorders, depression, or lack of self-confidence, and physical changes such as an increase in fat mass and a decrease in muscle mass (Traish, et al., 2009).

Testosterone

The T vasodilation and relaxation effect appears to be a modulation of smooth muscle ion channel function. Although it has been reported to exert these effects by inactivation of calcium channels operating with type L voltage in particular and/or activation of potassium channels activated by voltage-dependent calcium, there are no evidence studies for its effect on cavernosal smooth muscle cells. The available evidence is that in isolated corpora cavernosal strips, T leads to relaxation by activating potassium channels sensitive to adenosine triphosphate. (Podlasek, et al., 2016). While high T levels have antioxidant properties in the human prostate and rat nervous system, they can result in oxidation in rat and rabbit testicular tissues, rat muscles. Since the cell membranes in the testicular tissue are extremely rich in polyunsaturated fatty acids, they are extremely sensitive to oxidative stress. These findings are an indication that Tun has prooxidant effects in a texture- and sex-dependent manner (Aydilek et al. 2004).

Studies have reported that endogenous increase in serum T level or androgen therapy leads to an increase in secretory activity of seminal vesicles (SV) and seminal vesicle weight. SV has also been shown to have 5 alpha-reductase (5αR) activity, contains LH and human chorionic gonadotropin (hCG) receptors, and can be directly regulated by LH. SV receives sympathetic (from the superior lumbar and hypogastric nerves) and parasympathetic (pelvic plexus) innervation, and its secretory activity is also regulated by the

cholinergic and adrenergic nervous systems. Seminal vesicles are one of the sources of NO synthetase in men and increase NO production with muscarinic stimulation (Demir, 2019).

5 Alpha Reductase Enzyme

There are 3 subtypes of the 5aR enzyme; Type 1 is common in the body, while type 2 prostate and type 3 have been shown to be present in the brain, heart, and other organs besides androgen-dependent tissues such as smooth muscle and prostate (Amasyalı and Manav, 2016). Dose-dependent irreversible inhibition of the 5aR enzyme, the decrease in the level of DHT, which is responsible for phenotypic masculine characteristics, and the loss of masculine characteristics, partial deterioration in sexual functions, and decrease in sexual desire and libido, suggest that sexual functions are controlled by highly complex systems (Bortolato, et al., 2008).

With inhibition of the 5aR enzyme, erectile dysfunction occurs. Since there is no significant role in the ejaculation phase, no significant deterioration is observed in its deficiency (Balcı, et al., 2013). Inhibition of the 5aR enzyme; The drugs used (e.g. Finasteride acting on 5aRtip 2) are irreversible covalent binding in enzyme transcription or reducing the target organ response by blockade of the receptor (Marchetti, 2013). Enzyme-related medical agents; inhibitors are used in the treatment of hirsutism from an endocrinological point of view, urologically and oncological in prostate pathologies, and with other different effects in psychiatric and dermatological terms. (Marchetti, 2013).

Estrogen

Aromatase is an enzyme that catalyzes the conversion of T to estradiol. E2, on the other hand, acts on the hypothalamus with its negative feedback mechanism and reduces the release of LH and FSH, and therefore T. Substances such as flavonoids, caffeine, and zinc, which are found in the structure of many plants, are natural aromatase inhibitor substances. High doses and long-term consumption of these substances cause a decrease in E2 formation due to aromatase enzyme deficiency and a central increase in T, FSH, and LH levels due to insufficiency in the feedback mechanism (Oliveira, et al., 2012). There are many more publications that show the importance of the presence of E2 for the male gender. Observation of imbalances in the ratio between T and estradiol hormone in men is the main cause of diseases and aging. This disorder causes gynecomastia, testicular atrophy, palmar erythema, adiposity, decrease in muscle mass, benign 70-sided prostatic hypertrophy, mastopathy, hirsutism, cancer and infertility (Çalışkan, et al., 2016).

Aromatase Enzyme

Aromatase Enzyme inhibitors also play a role in this hypothalamic-pituitary-gonadal axis, reducing the hormone estradiol with antagonistic action, thus producing a gradual increase in FSH, LH, and T levels (Kaufman and Vermeulen, 2005). By ensuring that T, FSH, and LH levels return to normal values with the effect of an aromatase inhibitor, spermatogenesis is improved and used in the treatment of various diseases seen in men such as gynecomastia, early and delayed puberty, and prostatic hypertrophy (Roth, et al., 2008). It has been proven that the main problem in older men is T-E2 conversion. With the increase in fat mass due to age, there is also an increase in aromatase activity, as a result of which the level of estradiol increases and the T levels decrease, and therefore changes occur in the testicle and neuroendocrine system. By suppressing aromatase activity with medical agents, gonadotropin and T levels can be increased in elderly men (T'Sjoen, et al., 2005).

OTHER IMPORTANT NEURAL STRUCTURES

Estrogen And Androgen Receptors

For the expression of normal masculine sexual behavior, circulating free-form T is required to bind to androgen receptors (AR). However, a very small part of the T produced exists in free form and a very small amount of it is converted to E2 by the aromatase enzyme. The T, E2 receptor can bind to alpha and/or beta (ERα-ERβ). The presence of AR, Erα, and ERβ has been shown to be widely present in interconnected limbic regions such as the posteromedial component MeA of the medial lower division of the bed nucleus (BNST) of the stria terminal and the preoptic hypothalamus (POA). One study showed that mice or rats that degenerate ERα are infertile, ERβ inactive mice or rats do not have such abnormalities, and the ERα subunit is essential for fertility and reproduction (Macheroni, et al., 2020). The presence of ER is as important as the presence of AR in the stages of sexual development, and it has been shown that deficiencies in the congenital period can lead to bisexual or homosexual behavior in humans in adulthood, and even in similar ways in animals. In the behavioral patterns that take place during the sexual marrow process, the presence of ER (E2) has an important role in both arousal and erection-ejaculation cycle (Juntti, et al., 2010).

Male mating behavior has been shown to be inadequate in mice without the functional (ERα) alpha gene, spending little time and no preference on approaching and investigating behavior in stimulating female mice. To test the hypothesis that this lack of chemo-research behavior was due to the fact that males without the alpha gene were unable to detect and respond to female pheromones, males were exposed to chemosensory cues (dirty bedding) from females, after which females without the male alpha gene spent less time on chemo-examination and had similar responses to wild animals. Based on this data; It was concluded that the normal process between the neuroendocrine response and sexual behavior formation given to women was disrupted in mice without the alpha gene, and that while this gene was not required for responses to female pheromones, it was necessary for normal male sexual performance (Wersinger and Rissman, 2000).

Sex Hormone Bındıng Globulın

Sex hormone-binding globulin (SHBG) is synthesized by liver cells and has a high affinity for dihydrotestosterone (DHT) and T, Age-related androgen deficiency in the early stages of the testicular apparatus and other diseases, a decrease in the synthesis of sex hormones and, accordingly, the bioavailability rate usually leads to an increase in SHBG, which tends to retain total T in the blood for a period of time. The differential diagnosis of androgen deficiency at normal T levels, erectile dysfunction, and the diagnosis of sexual function of men should be looked at, especially in cases of inconsistency with laboratory indicators of the general male sex hormone level of clinical men. (Adlercreutz, et al., 1992; Peng, 2021).

Androgen Receptor Proteın

The androgen receptor protein (ARP) is expressed in Sertoli cells, and this is done by T stimulation. As a matter of fact, normally, as a result of the negative feedback mechanism of inhibin and T elevation and LH released from the Sertoli cell, it is expected to suppress the hypothalamic-pituitary axis by the santal route and to lower the T. In addition, in T central oscillation, there is an autonomic system, non-endogenous stimulation of central neural pathways (e.g., chemoreceptor activation of pheromones, stimulating sound frequencies from the female), and there must be high and prolonged T exposure in order to be suppressed by the increase in the periphery. On this occasion, we see once again the need for more work (Shah, et al, 2021).

NEUROTRANSMITTERS AND THEIR ROLE IN SEXUAL ACTIVITY

Sex hormones: E2, progesterone, and T act on neurotransmitters that modulate sexual behavior at the central and peripheral level, and these interactions imply complex modulation of sexual desire, sexual arousal, and orgasm (Boyarsky and Hirschfeld, 2000). As inhibitory mechanisms of action on sexuality in the studies conducted; anticholinergic, blockade of noradrenergic α-1 receptors, antihistaminergic, anitidopaminergic and elevated prolactin effects. An inhibitory effect on nitric oxide synthase (NOs) is also; It can directly affect sexual function through its binding to dopaminergic, cholinergic, histaminergic and α-adrenergic receptors, inhibition of cravings

and rewards, increased sedation and reduction of peripheral vasodilation (Yelboğa and Korgalı, 2015).

GABA

GABA is a neurotransmitter in the brain that suppresses nerve stimulation (inhibitor) and triggers sleep and sedation by suppressing the centers that provide staying awake. Tranquilizer drugs, such as benzodiazepines, perform their functions by increasing the effect of GABA in the brain (Üngüren, 2015). But this effect is dose-dependent; low-dose benzodiazepines may relieve sexual behavior because they reduce anxiety, but a high-dose inhibitory effect comes to the fore. There are disruptions in systems such as sexual functions, wakefulness, and perception. Therefore, it can be said that GABA both regulates and inhibits sexual function (Yelboğa and Korgalı, 2015). They suggested that an increase in GABAergic inhibitory effect in VMH suppressed glucagon and sympathoadrenal responses, leading to hypoglycemia, sweating, paresthesia, and dizziness, and autonomic insufficiency (Chan, et al., 2008).

Glutamate

Glutamate (Glu) nerve conduction in the central nervous system is regulated by astrocytes. Glucose is converted to Glu through the tricarboxylic acid cycle. Because neurons lack pyruvate carboxylase, a very important enzyme necessary in the tricarboxylic acid cycle, neurons are not able to produce Glu independently. In contrast, astrocytes can synthesize both Glu and its metabolic precursor, glutamine (Gln). Gln, on the other hand, is transported to neurons where it can be converted to Glu or GABA. The expression of Fos, a protein that is considered an early indicator of cell activity, is higher in sexually experienced men compared to sexually naïve men. In a study examining whether being sexually experienced or inexperienced, the number of astrocytes in MPOA was associated with ejaculation delay, as well as the duration of the post-ejaculation interval, it was shown that astrocyte count was negatively associated with the delay in reaching ejaculation in sexually inexperienced rats, but there was no relationship in sexually experienced rats. These data show that astrocyte induced Glu release initially has a role in the modulation of sexual behavior, but with sustained sexual experience, glutamatergic projections from other brain regions such as BnST and MeA

become the dominant modulators, and glutamatergic innervation of mPOA changes as a function of sexual experience (Will, et al., 2015).

Glu levels increase during sexual activity, peak during ejaculation, and gradually decrease after ejaculation. Lower levels of Glu after ejaculation translate into longer post-ejaculation intervals, i.e., the magnitude of the Glu decrease following ejaculation is directly linked to the prolongation of the duration of the post-ejaculation interval. The application of Glu reuptake inhibitors to the medial preoptic area (mPOA) of the hypothalamus reverses the system and increases the number and frequency of ejaculations that a male rat achieves during a mating period, and shortens the latency of ejaculation, that is, a decrease in high Glu, EL and PEI values. There are publications that Gln in MPOA can elicit genital reflexes in anesthetized rats and that Glu receptor antagonists, i.e. a decrease in Glu action, in MPOA disrupt mating. In a study to assess Glu levels in MPOA, a slight increase in extracellular Glu was found when the male rat was presented with a female, a significant increase in insertion and penetration periods, and a very large increase in samples collected during ejaculation. After the first ejaculation, there was a sudden drop in levels; the magnitude of this decrease was highly correlated with the length of the PEI period. Administrations of a Glu reuptake inhibitor to MPOA before and during mating increased the level of extracellular Gln and the number of calculations monitored during the 40-minute test while decreasing its EL and shortening the duration of PEI to maintain mating. In MPOA, Gln was found to be an important facilitator of mating, and the decline in Glu after ejaculation regulated PEI regulation (Dominguez, et al., 2006).

VMH neurons receive both γ-amino butyric acid (GABA)-ergic and glutamatergic innervation and control the activity of the autonomic nervous system. Another study stated that presynaptic modulation of stimulatory glutamatergic transmission would play an important role in the regulation of various behavioral functions mediated by VMH. VMH integrates front brain neuronal input with information from the brainstem and sends output to many brain regions, including the medial and lateral hypothalamus. It has been suggested that activation of the hypothalamic glutamatergic system induces autonomic nerve symptoms such as bradycardia and hypotension (Lee, et al., 2007).

Nitric Oxıde

Nitric oxide (NO) is synthesized from L-Arginine by "NO synthase" (NOS), which is extensively present in the limbic system in the brain and penile tissue and performs relaxation in smooth muscles and dilatation of the vascular endothelium via the c-GMP intracellular signaling transmitter. In this respect, they have an important role in the initiation and maintenance of erection and in the transition to the post-ejaculatory phase. NO is not a stored substance but is broken down by the phosphodiesterase enzyme in the cells, it acts in the genital area immediately after use. Phosphodiesterase inhibitors (for example, sildenafil) are used in the treatment of erectile dysfunction for this purpose (İncesu, 2004). Androgens have been shown to increase NOS expression in penile corpus cavernosum in rats, while DHT has been shown to be more effective than T in increasing NOS expression (Pinsky, 2011).

In a study investigating the role of NO-cGMP pathway in the regulation of MPOA, DA and mating in male rats; The application of a Soubl guanilate cyclase inhibitor had the effect of blocking mating and facilitating the activator. The presence of NO has been shown to be an important regulator of neurochemical and neuroendocrine signaling and to play a positive role on both peripheral and central nervous systems in terms of sexual functions (Sato and Hull, 2006).

In a study examining the distribution and activity of NOS-containing neurons in the mating behavior circuits of the male Syrian hamster brain, it was shown that many NOS-positive neurons in the lower back of MeA contained androgen receptors of MPOA and ventral premamiller nucleus, and that only NOS-positive neurons in MPN decreased after castration. With these results, it was concluded that gonadal steroids have an effect on NO production in certain regions of the central nervous system, but some regions can make their own NO production independently of gonadal T effect (Hadeishi and Wood, 1996). In a research; Microinjection of L-nitro-arginine methyl ester (L-NAME, a NO synthesis inhibitor) into MPOA has been shown to block mating in rats with little sexual experience and disrupt mating in sexually experienced males (Lagoda, et al., 2004).

This result showed that the presence of NO in MPOA was highly important for mating and stimulus sensitivity in male rats. It would also not be wrong to conclude that as sexual experience increases, processes that have a

negative impact on sexual behavior cause less harm than those of the relatively inexperienced. Tissue levels of the neurotransmitter reflect release as well as synthesis. In a study evaluating whether castration affected the number of NO-producing cells in MPOA, there was no short-term effect, but long-term castration subjects showed a significant reduction in the number of NADPH-d (nicotinamide adenine dinucleotide phosphate diaphorase) positive neurons in the medial preoptic nucleus (MPN) and brain NO synthase immunoreactive (bNOS-ir) neurons. Long- or short-term castration showed no effect on the number of bNOS-ir neurons in the paraventricular nucleus (PVN) or MeA, but short-term castration reduced bNOS-ir neurons in the BNST bed nucleus. As a result, all these data have shown that; While the decreases in the free T level produced gonadally do not have a significant effect on the central plant, the effect of NO decreases in peripheral tissue. T activates male sexual behavior by increasing the production of NO in MPOA, thereby increasing the release of DA (Du and Hull, 1999).

Dopamıne

Dopamine (DA) facilitates male sexual behavior in all species studied, including rodents and humans. In one study, DA agonists microinjected into MPOA facilitated sexual behavior, while DA antagonists disrupted mating, genital reflexes, and sexual motivation. DA can remove tonic inhibition in MPOA, thereby increasing sensorimotor integration and also coordinating autonomic effects on genital reflexes. In addition to sensory stimulation, T, NO, and Glu are other factors that influence DA release in MPOA. (Dominguez and Hull, 2005).

The release of DA in MPOA of the hypothalamus is an important facilitator of male sexual behavior. The presence of a receptor female increases extracellular DA in MPOA, which increases even more during mating. However, the neurochemical events that mediate the increase in DA in MPOA are not fully understood. Here, glutamate administered to MPOA increased extracellular DA while administration of NOS inhibitors prevented this increase. However, it has been stated that extracellular concentrations of DA parent metabolites are reduced by Glu, which may be due to the inhibition of the DA transporter. These results were increased by Glu's extracellular DA in

MPOA through NO, stimulating NOS activity, and by glutamatergic stimulation, with female exposure in MPOA (Dominguez, et al., 2004).

Dopamine (DA) is released in the MPOA of male rats shortly before and during mating. The T metabolite 17beta-estradiol is responsible for maintaining MPOA basal extracellular DA levels and provides DA release from its stores by reporting it to MPOA when DA needs it. Studies have reported that the content of DA stored in MPOA tissue is greater in castrated male rats than in gonadally intact males, but less in its extracellular form. (Putnam, et al., 2005). In short, the peripheral is also decreasing as the emission from the central tanks' decreases. Since T and its metabolite, E2, are not present in the absence of testicular tissue, the release of DA is disrupted, and the extracellular DA is reduced. The fact that E2 is not completely depleted may be due to the presence of a slight release of T from the adrenal gland. The T metabolite E2 increases neuronal NO synthase (nNOS) in MPOA (DHT is not effective here), thus increasing NO.

In those who are castrated and not T, DHT decreases, as it will not be converted to DHT. While we expect a decrease in DA storage in MPOA due to this, the fact that the depot DA is higher in castrations on the contrary in the studies can be explained by the relative increase in the storage rate in the absence of the release of DA. All these data have shown us once again how important the presence of NO DA çeliand E2 is on sexual functions. It has also shown that the presence of T on sexual functions is necessary for certain stages and that the absence of testicular tissue is tried to compensate partially for adrenal-derived T (Putnam, 2005).

Cholecystokının

Cholecystokinin (CCC) is a neuropeptide that plays a role in the digestive system as well as a neurotransmitter or neuromodulator in the central nervous system and in the digestive system. Enteroendocrine cells in the mucous layer of the small intestine are secreted by brain neurons and neurons of the enteric nervous system. The CCKa receptor subtype in the Accumbens nucleus has been shown to potentiate the behavioral and neurophysiological effects of DA and the mesolimbic DA system is involved in the regulation of male rat sexual behavior. One study also showed that electrical stimulation of the ventral tegmental region greatly improved several appetizing and complementary

measures of male rat sexual behavior, while administration of a CCKa receptor antagonist to the posteromedian nucleus reversed the development of electrically stimulated behavior, but the CCKb antagonist had no effect in these areas. In the anterolateral nucleus, the effect of increasing the sexual response produced by electrical stimulation was reversed by the administration of CCKa and CCKb antagonist (Markowski and Hull, 1995).

Reactıve Oxygen Radıcals

Free radicals in general, especially reactive oxygen radicals, accumulate in living cells and lead to the formation of oxidative stress. It is well known that oxidative stress causes damage to cells, reduces cell function, For example, there are many publications that it reduces both enzymatic and non-enzymatic antioxidant reservoirs in Leydig cells in the testicles, causes tissue damage and leads to a decrease in T synthesis and therefore serum T level (Nasrolahi, et all., 2013). ROS is a reactive and unstable byproduct of normal metabolism and exerts a toxic and degenerative effect on biomolecules. High T levels are necessary for sexual processes in terms of the balance of oxidative stress increased by ROS production on genital tissues and gonads and minimizing the risk of damage to antioxidant defense mechanisms. However, both many different factors and the continuous continuation of biological cellular activity enter a vicious circle in favor of increasing ROS accumulation over time and lose their effectiveness in these protective mechanisms with advancing age.

The unusually high concentration of polyunsaturated fatty acids in the plasma membrane of germ cells makes them vulnerable to free radical oxidation, and oxidative stress mediated by reactive oxygen/nitrogen species (ROS/RNS) in these cells plays a role in the pathogenesis of lipid peroxidation (LPS). Structural changes in both histopathologic and DNA have been observed in the testicular tissues of rats exposed to LPS has been shown to increase lipid peroxides by accelerating the formation of NO and prostaglandins and to cause deterioration in the functional integrity of functional organelles of the rat testicle, such as Sertoli cell. Under normal physiological conditions, free radicals are produced in the subcellular compartments of the testicles, but they are inactivated by physiological mechanisms (Doğanyiğit, 2019).

Studies have defined adolescence as the period of sexual maturation and stated that behavioral and psychopharmacological changes specific to this

period are seen. In line with this criterion, the adolescent period in rats fits between approximately 30 and 42 days after birth. In a study, in the prefrontal cortex and hippocampus of adolescent rats; superoxide dismutase enzyme activity and levels of substances reacting with thiobarbituric acid increased, while glutathione peroxidase activity decreased. In the adolescent striatum; superoxide dismutase enzyme activities and levels of substances reacting with thiobarbituric acid were found to be lower than adults. These results suggest that in the adolescent rat brain, the prefrontal cortex and hippocampus regions are more vulnerable to oxidant stress than in other periods and have different mechanisms, despite increased experience with age (Uysal, et al., 2005).

Dıabetes Mellıtus

Diabetes has a negative effect on male sexual function, the weight of the genitals, and sperm production, with a parallel decrease in the level of T. Male sexual dysfunction caused by diabetes, is associated with endothelial dysfunction and its inhibition is known to affect diabetes by improving endothelial function (Minaz, et al., 2019). The regulatory effect of sex hormones against glucose homeostasis and hypoglycemia occurs through the VMH nucleus of the hypothalamus. VMH contains neurons that perceive glucose, which increases their activity as glucose increases (stimulated by glucose) or decreases (inhibited by glucose). Selectively suppressing E2 receptor activity in VMH causes an increase in circulating glucose levels. Also, the electrophysiological recordings in VMH showed a sexual dimorphism with the stimulation of neurons inhibited by glucose, not neurons stimulated by glucose; male mouse neurons increased their excitability at generally lower glucose concentrations compared to female mice (Khodai, and Luckman, 2021).

Age

For mammals, the term "adult" represents quite different time intervals and ages between species. Although rodents can reproduce sexually from about five weeks of age, their patterns of sexual behavior and sexual maturity can take a long time to reach. It is stated in many sources that in experimental studies the definition of 'adult' refers to the sexual maturity of the rodent, and a 2-3 month old rat is suitable in this respect. However, it has been shown by many studies that as the rate of sexual experience increases, neuroplasticity develops

in the central nervous system, which has quite different results on neurohormonal parameters and sexual behavior than those who are inexperienced (Jackson, et al., 2017).

KAYNAKÇA

Adlercreutz, Herman, et al. (1992). Dietary phytoestrogens and cancer: in vitro and in vivo studies." The Journal of Steroid Biochemistry and Molecular Biology 41(3-8): 331-337.

Ahlenius, S., Heimann, M., Larsson, K. (1979). Prolongation of the ejaculation latency in the male rat by thioridazine and chlorimipramine. Psychopharmacology (Berl). (2):137-40. doi: 10.1007/BF00433039. PMID: 117481.

Atan, A., and Tuncel, A. (2013). Mechanism of pain after male genitourinary system surgeries and treatment approaches." New Journal of Urology - The New Journal of Urology, 8 (1): 72-76.

Amasyalı, A. S., and Manav, A. N. (2016). Effects of five alpha reductase inhibitors on sexual function. Andrology Bulletin, 65:99-103.

Aykan, S., Gönültaş, S., Yılmaz, M., & Dinçer, M. M. (2017). Gecikmiş orgazm ve anorgazmi. Androloji Bülteni, 19(4):131-137.

Aykan, Serdar, et al. "Delayed orgasm and anorgasmia." Andrology Bulletin 19.4 (2017): 131-137.

Balcı, M., Tuncel, A., Atan, A. (2013). Effects of 5-α reductase enzyme inhibitors on male sexual functions (Review). Andrology Bulletin, 15(54):176-179.

Bialy M., Bogacki-Rychlik, W., Przybylski, J., Zera, T. (2019). The Sexual Motivation of Male Rats as a Tool in Animal Models of Human Health Disorders. Frontiers in Behavioral Neuroscience, 13: 257–. doi:10.3389/fnbeh.2019.00257.

Bortolato, M., Frau, R., Orru, M., et al. (2008). Antipsychotic-like properties of 5-α-reductase inhibitors. Neuropsychopharmacology, 33(13): 3146-3156.

Boyarsky, B.K., Hirschfeld, R.M. (2000). The management of medication-induced sexual dysfunction. Essent Psychopharmacol, 3: 39-58.

Cabadak, H. (2006). Distribution of Muscarinic Acethylcholine Receptors And Related Signal. Turkish Journal of Biochemistry Turk J Biochem 31 (3): 141–150.

Chan, O., Cheng, H., Herzog, R., et al. (2008). Increased GABAergic tone in the ventromedial hypothalamus contributes to suppression of

counterregulatory responses after antecedent hypoglycemia. Diabetes, 57:1363–70.

Çalışkan, U., Durbilmez, G. D., Memiş, G. (2016). Phytotherapeutics effective on benign prostatic hyperplasia. Journal of Faculty of Pharmacy of Ankara University, 43(2): 173-196.

Demir, I. (2019). Effects of intracerebroventricular salusin-β infusion on the hypothalamus-pituitary-testicular axis in rats. Master's Thesis. İnönü University Institute of Health Sciences.

Doğanyiğit, Z., Silici, S., Kaymak, E. (2019). Determination of the Protective Role of Apilarnil Against Testicular Toxicity Due to Lipopolysaccharide (LPS) in Male Rats. Bozok Tıp Dergisi, 9(2): 146-154.

Dominguez, J.M., Gil, M., Hull, E.M. (2006). Preoptic glutamate facilitates male sexual behavior. J Neurosci. 26(6):1699-703. doi: 10.1523/JNEUROSCI.4176-05.2006.

Dominguez, J.M., Hull, E.M. (2005). Dopamine, the medial preoptic area, and male sexual behavior. Physiol Behav, 86(3):356-68. doi: 10.1016/j.physbeh.2005.08.006.

Dominguez JM, Hull EM. (2001). Stimulation of the medial amygdala enhances medial preoptic dopamine release: implications for male rat sexual behavior. Brain Res. 917(2):225-9. doi: 10.1016/s0006-8993(01)03031-1.

Du, J., Hull, E.M. (1999). Effects of testosterone on neuronal nitric oxide synthase and tyrosine hydroxylase. Brain Res. 836(1-2):90-8. doi: 10.1016/s0006-8993(99)01618-2. PMID: 10415408.

Üngüren E. (2015). The Impact of Neuroanatomical and Neurochemical Structure of Brain on Personality and BehaviorInternational Journal of Alanya Faculty of Business, 7(1):193-219.

Georgiadis, J. R. (2015). Functional neuroanatomy of human cortex cerebri in relation to wanting sex and having it. Clinical Anatomy, 28(3), 314-323.

Gil, M., Bhatt, R., Picotte, K.B., Hull, E.M. (2013). Sexual experience increases oxytocin receptor gene expression and protein in the medial preoptic area of the male rat. Psychoneuroendocrinology. 38(9):1688-97. doi: 10.1016/j.psyneuen.2013.02.002.

Hadeishi, Y., Wood, R.I. (1996). Nitric oxide synthase in mating behavior circuitry of male Syrian hamster brain. J Neurobiol. 30(4):480-92.

Hakan, Ş., Muammer, K. (2016). Male Sexual Health-Delayed Ejaculatıon, Andrology Bulletin 18(65): 92–98.

İncesu, C. (2004). Sexual functions and sexual dysfunctions. Journal of Clinical Psychiatry 3: 3-13.

Jackson, S. J., Andrews, N., Ball, D., et al. (2017). Does age matter? The impact of rodent age on study outcomes. Laboratory animals, 51(2): 160-169.

Juntti, S.A., Tollkuhn J., Wu, M.V., et al. (2010). The androgen receptor governs the execution, but not programming, of male sexual and territorial behaviors." Neuron 66(2): 260-272.

Kaufman, J.M., Vermeulen, A: (2005).The decline of androgen levels in elderly men and its clinical and therapeutic implications. Endocr Rev 26:833-876.

Khodai, T., & Luckman, S. M. (2021). Ventromedial nucleus of the hypothalamus neurons under the magnifying glass. Endocrinology, 162(10):bqab141.

Lagoda G, Muschamp JW, Vigdorchik A, Hull EM. (2004). A nitric oxide synthesis inhibitor in the medial preoptic area inhibits copulation and stimulus sensitization in male rats. Behav Neurosci. 118(6):1317-23. doi: 10.1037/0735-7044.118.6.1317.

Lee JG, Choi IS, Park EJ, et al. (2007). b2-Aadrenoceptor-mediated facilitation of glutamatergic transmission in rat ventromedial hypothalamic neurons. Neuroscience 144:1255–65.

Lee, H., Kim, D. W., Remedios, R. (2014). Scalable control of mounting and attack by Esr1+ neurons in the ventromedial hypothalamus. Nature, 509(7502): 627-632.

Lee, H., Kim, D.W., Remedios R., et al. (2014). Scalable control of mounting and attack by Esr1+ neurons in the ventromedial hypothalamus. Nature, 509(7502): 627-632.

Lorrain DS, Matuszewich L, Friedman RD, Hull EM. (1997). Extracellular serotonin in the lateral hypothalamic area is increased during the postejaculatory interval and impairs copulation in male rats. J Neurosci. 1;17(23):9361-6. doi: 10.1523/JNEUROSCI.17-23-09361.1997.

Macheroni C, Lucas TFG, Porto CS. (2020). The role of estrogen receptors in rat servoli cells at different stages of development. Helion 6:e05363. doi: 10.1016/j.helion.2020.e05363.

Maffei, M. (2021). 5-Hydroxytryptophan (5-HTP): Natural Occurrence, Analysis, Biosynthesis, Biotechnology, Physiology and Toxicology. International Journal of Molecular Sciences. 22:181. 10.3390/ijms22010181.)

Marchetti, P.M., and Barth, H.J. (2013). Clinical biochemistry of dihydrotestosterone. Annals of Clinical Biochemistry 50.2: 95-107.

Markowski, V.P, Hull, E.M. (1995). Cholecystokinin modulates mesolimbic dopaminergic influences on male rat copulatory behavior. Brain Res. 699(2):266-74. doi: 10.1016/0006-8993(95)00918-g.

Minaz, N., Razdan, R., Hammock, B. D., et al. (2019). Impact of diabetes on male sexual function in streptozotocin-induced diabetic rats: Protective role of soluble epoxide hydrolase inhibitor. Biomedicine & Pharmacotherapy, 115: 108897.

Nasrolahi, O., Khaneshi, F., Rahmani, F., & Razi, M. (2013). Honey and metformin ameliorated diabetes-induced damages in testes of rat; correlation with hormonal changes. Iranian journal of reproductive medicine, 11(12):1013.

Oliveira, G. A. R., Ferraz, E. R. A., Souza, A. O., et al. (2012). Evaluation of the mutagenic activity of chrysin, a flavonoid inhibitor of the aromatization process. Journal of Toxicology and Environmental Health, Part A, 75(16-17):1000-1011.

Peng, Meng-fan, Tian, S., Song, YA-G., et al. (2021). Effects of total flavonoids from Eucommia ulmoides Oliv. leaves on polycystic ovary syndrome with insulin resistance model rats induced by letrozole combined with a high-fat diet." Journal of Ethnopharmacology 273:113947.

Pinsky MR, Gur S, Tracey AJ, Harbin A, Hellstrom WJ. The effects of chronic 5-alpha-reductase inhibitor (dutasteride) treatment on rat erectile function. J Sex Med. 2011 Nov;8(11):3066-74.

Podlasek, C.A.; Mulhall, J.; Davies, K.; et al. (2016). Translational Perspective on the Role of Testosterone in Sexual Function and Dysfunction. The Journal of Sexual Medicine, 13(8):1183–1198. doi:10.1016/j.jsxm.2016.06.004.

Putnam, S.K., Sato S., Riolo, J.V., Hull, E.M. (2005). Effects of testosterone metabolites on copulation, medial preoptic dopamine, and NOS-

immunoreactivity in castrated male rats. Horm Behav. (5):513-22. doi: 10.1016/j.yhbeh.2005.01.007.

Roth, M.Y, Amory, J.K, Page, S.T. (2008). Treatment of male infertility secondary to morbid obesity. Nat Clin Pract Endocrinol Metab. 4:415-9.

Sato, S.M, Hull, E.M. (2006). The nitric oxide-guanosine 3',5'-cyclic monophosphate pathway regulates dopamine efflux in the medial preoptic area and copulation in male rats. Neuroscience. 139(2):417-28.

Shah, W., Khan, R., Shah, B., et al. (2021). The Molecular Mechanism of Sex Hormones on Sertoli Cell Development and Proliferation. Frontiers in Endocrinology 12: 648141

Shimura T, Yamamoto T, Shimokochi M. (1994). The medial preoptic area is involved in both sexual arousal and performance in male rats: re-evaluation of neuron activity in freely moving animals. Brain Res. 640(1-2):215-22. doi: 10.1016/0006-8993(94)91875-9.

Çelik, S., Kılıç, K.D., Yiğittürk, G., (2017). The current situation in penile transplantation; a morphological evaluation. Istanbul Bilim University Florence Nightingale Journal of Transplantation 2(1): 34-44.

Stephen Stahl, S.M. (2008). Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. third edition. New York: Cambridge University Press.

Traish, A.M., Guay, A., Feeley, R., Saad, F. (2009). The dark side of testosterone deficiency: I. Metabolic syndrome and erectile dysfunction J Androl 30(1):10–22. https://doi.org/10.2164/jandrol.108.005215.

T'sjoen, G.G., Giagulli, V.A., Delva, H. (2005). Comparative assessment in young and elderly men of the gonadotropin response to aromatase inhibition. J Clin Endocrinol Metab. 90:5717– 22.

Turkmen, M., Akcay, G. (2009). Evaluation of Autonomic Nervous System Functions in Endocrine System Diseases by Sweat Test, Specialty Thesis Erzurum.

Uysal, N., Gönenç, S., SönmeZ, A., et al. (2005). Antioxidant enzyme activities and lipid peroxidation levels in adolescent rat brain. Ege Tıp Dergisi, 44:75-79.

Wersinger, S.R, Rissman, E.F. (2000). Estrogen receptor alpha is essential for female-directed chemo-investigatory behavior but is not required for the pheromone-induced luteinizing hormone surge in male mice. J

Neuroendocrinol. 12(2):103-10. doi: 10.1046/j.1365-2826.2000.00418.x.

Wersinger, S.R, Rissman, E.F. (2000). Dopamine activates masculine sexual behavior independent of the estrogen receptor alpha. J Neurosci. 20(11):4248-54.

Will, R.G., Nutsch, V.L., Turner, J.M, (2015). Astrocytes in the medial preoptic area modulate ejaculation latency in an experience-dependent fashion. Behav Neurosci. 129(1):68-73. doi: 10.1037/bne0000026.

Yardımcı, A. (2015). Antidepresan olarak kullanılan bupropiyon, paroksetin ve agomelatinin erkek sıçanlarda puberteye geçiş üzerindeki etkileri/Effects of paroxetine, bupropion and agomelatine, which are used as antidepressants, on puberty onset in male rats. 2015.

Yelboğa, Z, Korgalı, E. (2015). Psychopharmacology and sexual function (Review); 17(62): 189-193.

CHAPTER 15

ANAMNESIS IN GERIATRIC PATIENTS

Asst. Prof. Dr. Şeyda Tuba SAVRUN[1]
Assoc. Prof. Dr. Atakan SAVRUN[2]
Emergency Medicine Physician Rahime Şahin TURAN[3]
Res. Asst. Elif Yaren KURUL[4]
Res. Asst. Elif UĞUR[5]

[1] Ordu University, Faculty of Medicine, Emergency Department, Ordu, Türkiye. dr.seyda.tuba@gmail.com, Orcid ID: 0000-0002-6512-2987
[2] Ordu University, Faculty of Medicine, Emergency Department, Ordu, Türkiye. atakan4601@hotmail.com, Orcid ID: 0000-0001-7468-4159
[3] Ordu University Training and Research Hospital, Emergency Service, Ordu, Türkiye. drrahime28@hotmail.com, Orcid ID: 0000-0002-8067-2944
[4] Ordu University, Faculty of Medicine, Emergency Department, Ordu, Türkiye. yarenkurul1996@hotmail.com, Orcid ID: 0000-0001-9024-7346
[5] Ordu University, Faculty of Medicine, Emergency Department, Ordu, Türkiye. elfuugur@hotmail.com, Orcid ID: 0000-0001-9655-8591

Inroduction

Positive developments in the field of medicine have contributed positively to the life span of people. According to the World Health Organization (WHO), while 12% of the population was 60 years and older in 2015, it is estimated that this rate will increase to 22% in 2050(1). Similarly, with the ageing of the population in our country, the majority of the treated patients are patients older than 65 years of age. According to the 2021 data of Turkstat, while the population of people 65 and over was 6 million 651 thousand 503 people in 2016, it was reported that it increased to 8 million 245 thousand 124 people in 2021. When the distribution of the elderly population in our country by age group is examined, it has been determined that 64.7% of the elderly population is in the 65-74 age group, 27.3% is in the 75-84 age group, and 8.0% is in the 85 and over age group. Compared to middle-aged adults, patients over the age of 65 are more likely to visit outpatient clinics and be more likely to be hospitalized (2,3)

While evaluating patients over 65 years of age, as in all age groups; history and physical examination are very valuable. Especially taking a good and quality anamnesis is an art and a skill that every physician should have. The first step on the path to diagnosis depends on the anamnesis. It is valuable to take a good anamnesis for the correct diagnosis. However, it is not always easy to take anamnesis and perform a physical examination in the geriatric population compared to other age groups. In this direction, modifying our traditional anamnesis and physical examination methods according to the geriatric population may provide a solution for patients in this group (3)

Medical History

As in all age groups, it is very important for the physician to gain the confidence of the patient in the geriatric age group. For this purpose, the physician's introducing himself before starting the first evaluation increases the quality of communication with the patient and increases the patient's sense of trust. The fact that the patient examination room is bright and spacious is among the factors that have a positive effect on the patient at the initial evaluation stage. In addition, skin-to-skin

contact, such as holding the patient's hand or lightly touching his shoulder, positively affects communication with patients.

While evaluating the patient, first of all, the main complaint and the conditions and symptoms that bother him should be questioned. In addition, the duration and course of symptoms should be specifically investigated. Chronic diseases, past medical history, occupational history, social history and family history should be questioned. In addition, systemic symptoms should be questioned extensively to detect additional complaints.

It is very valuable to pay attention to the mental functions of the patient while evaluating the patient. Evaluation should continue, taking into account the capacity to understand and answer the questions asked. Offensive, criticizing speech and behaviour should be avoided when the patient is alone or in the presence of his relatives. On the contrary, it is necessary to ensure that the patient expresses his/her complaints directly by displaying an attitude that increases the patient's self-confidence.

The patient's hearing and vision impairment, restricted mobility, and slowed reaction time should be considered. In this direction, the physician should be more patient by paying attention to the patient's speaking rate, the level of his voice and the time he will spare for the patient (4).

Drug History

Polypharmacy is observed very frequently in the geriatric population. In a study conducted in our country, it was reported that 90% of individuals over the age of 65 had one, one, 35% had two, 23% had three and 14% had four or more chronic diseases (5).The number of tablets, injections or herbal medicines used by the patient, frequency of use, duration and who started it should be questioned. Again, in a study conducted in our country, it was reported that 21.1% of the population used drugs by their own decision, 13.2% with the recommendation of a friend, 7.9% with the advice of a pharmacist, and 5.2% with the recommendation of a neighbour (6). It should be learned whether he has developed an allergy or intolerance to any drug in the past.

Nutritional History

Nutrition is one of the most basic human needs and is essential for a healthy life. Nutritional deficiency, especially insufficiency in protein intake, is very common in people over 65 years of age. More than 60 per cent of elderly people are malnourished, and because there are many causes of malnutrition, it can be difficult to distinguish between age-related and pathological. Obtaining detailed information about the diet of our patients and guiding our patients can provide a solution to this situation. As a result, proper nutrition is an important aid in preventive medicine in geriatric patients (7).

Mental Status Anamnesis

Although it can be understood from the patient's speech and style, it is more reliable to evaluate the mental state with cognitive status tests. In addition, it is important to evaluate and record the mental state with tests to detect mental function changes in the future. In addition, patients' depression, substance use status, side effects of prescribed drugs, and the effects of other medical conditions on mental status should be considered (8).

Functional History

A functional evaluation includes the patient's ability to perform various tasks in daily life such as dressing, housework, and shopping. Because the ability to do their job is closely related to the quality of life, and its analysis forms the basis of geriatric analysis. Functional status may signal a disease. Functional status is also associated with the need for institutionalization and mortality (9)

Social History

Elderly people often present with difficulties related to daily life and detailed questioning is required, including the patient's family. In some cases, the caregiver also plays an important role in the patient's health. At the same time, the patient's financial situation can affect the patient's health, nutrition and living conditions at home. For this reason, information about the patient's social security and financial status should be obtained (10).

Examination in Geriatric Patients

Physical examination is very important in geriatric patients as in all age groups. Before starting to examine the patient, care should be taken to ensure that the examination environment is suitable for patient privacy. Also, care should be taken that the ambient temperature is neither too hot nor too cold.Balance problems are common in geriatric patients due to the physiopathological changes that occur with aging. For this reason, care should be taken that the examination table of geriatric patients who are prone to falling is protected against the danger of falling, and that the geriatric patient is not left alone in the examination room.In addition, due to the slow physical activity of geriatric patients, the duration of the physical examination may be prolonged. For this reason, it is necessary for the physician to be patient and not rush to examine the patient.The physical examination starts from the first time the patient is seen.For this reason, the patient's posture, speech style and facial expressions give the physician the first clues about the patient (11).

Vital signs

Geriatric patients are a patient group prone to malnutrition.For this reason, the height and weight of the geriatric patient group should be measured at each examination.Replacement therapy in fluid-electrolyte disorders should be planned according to the weight of the patient.

When measuring the blood pressure of the patients, blood pressure should be measured in both arms. In case of doubt, a difference in blood pressure may bring to mind aortic dissection. In addition, the blood pressure of the patients should be measured separately in both standing and sitting positions. The low blood pressure measured in the standing position helps us to diagnose orthostatic hypotension. Orthostatic hypotension is more common in the elderly than in the normal population. In fact, it has been reported in the literature that 30% of the elderly over 65 years of age have orthostatic hypotension (12). Similarly, the evaluation of the patients pulse should be done on both arms.

A respiratory rate of between 16 and 25 per minute is considered normal. If the respiratory rate per minute exceeds 25, in the patient; It is necessary to consider diseases such as sepsis, decompensated heart

failure, lower respiratory tract infection, pulmonary embolism. If the oxygen saturation is below 92%, it is necessary to consider that the patient has COPD and asthma.If these diseases are not known, we should think that it is a new clinical picture that develops acutely. Examples of these clinical pictures are pneumonia, decompensated heart failure, pulmonary embolism, pneumothorax. In addition, unlike non-geriatric patients, the absence of fever in patients in this group does not always exclude infection (13).

Head and Neck Examination

In this type of examination, the head, mouth, pharynx, eyes, ears, nose and neck regions of the patients are evaluated. The examination consists of inspection and palpation stages. With head inspection, the shape, symmetry and size of the area examined are examined. Palpation is performed starting from the frontal area and covering the entire scalp. The presence of any nodules, swelling, tenderness is investigated. In the oral examination, the lips, mucous membrane, teeth and gums, and uvula are evaluated. In patients using dentures, intraoral wound should be examined.In the nasal examination, the presence of septal deviation, nasal discharge, bleeding, swelling is investigated. In eye examination, visual acuity, visual field, eye movements are evaluated. Finger counting for visual acuity is a more suitable method for elderly patients. Thyroids in the neck are palpated and evaluated for nodules and masses. Jugular venous distention is evaluated, if present, it is necessary to be careful in terms of pericardial tamponade. Also, the carotid arteries are auscultated, and the presence of a murmur may explain many of the symptoms (14).

Chest Examination

Chest examination first begins with inspection. It should be evaluated in terms of kyphosis, scoliosis, and barrel chest. When evaluating patients by palpation, it is very important to investigate the sensitivity of the vertebrae, the presence of anatomical deformities, and the presence of subcutaneous crepitation, especially in trauma patients. While evaluating patients with auscultation during chest examination, each area should be auscultated. In patients with auscultation

examination; diagnoses such as pneumonia, pneumothorax, decompensated heart failure, pulmonary edema can be made to a large extent.

In the lung examination of the adult age group, rales in the lung bases suggest the diagnosis of heart failure, while this examination finding may be normal in geriatric patients, and it is expected to disappear after deep breathing (15).

Cardiovascular System Examination

Heart rate, rhythm, and murmurs should be evaluated during cardiac auscultation. The most common type of murmur in the elderly is a systolic murmur. The most common cause is aortic valve sclerosis. These murmurs rarely spread to the carotids and do not cause much clinical concern to the physician. Aortic stenosis is another cause of systolic murmur. Aortic stenosis is a condition that increases with age and has a high mortality and morbidity rate.

If left untreated and/or symptomatic severe aortic stenosis, the mortality rate is high. Another type of murmur is the diastolic murmur. Pulse examination is very important in geriatric patients. Pulse evaluation of arteries such as temporal, carotid, brachial, radial, femoral, popliteal, dorsalis pedis and tibialis posterior should be done bilaterally.

In case of clinical suspicion, Doppler USG should be performed and both arterial and venous structures should be evaluated (16,17).

Abdominal Examination

As in other age groups, abdominal examination of geriatric patients should be started with inspection. The shape and symmetry of the abdomen of the patients, if any, surgical scars, spider angioma, etc. should be evaluated. Especially the asymmetry in the abdomen is important for sigmoid volvulus. While palpation examination of the abdomen is performed, the area with pain should be palpated last. Tenderness, rebound sign and defense status should be investigated in the sensitive area. Rebound sign is a sign of peritoneal irritation and is a valuable examination finding in terms of acute abdomen. All quadrants should be palpated. Particular attention should be paid to the dimensions of the liver and spleen when palpating. Inguinal canals and femoral

triangles should be evaluated for hernia. In addition, it should not be forgotten that the suprapubic region should be evaluated in terms of sensitivity and pain (18).

Genitourinary System

Findings such as fissure, hemorrhoids, anal sphincter tone, fecaloma, rectal tumors, prostatic hypertrophy can be detected by genitourinary system examination. It should be evaluated in terms of rectal prolapse, vaginal prolapse and cystocele, especially in postmenopausal women. Geriatric men, prostate tissue should be palpated and examined for prostate hypertrophy and prostate cancer (18).

Musculoskeletal System

As in other system examinations, inspection of the musculoskeletal system should begin with inspection.

It is important to observe the posture, gait and movements of the patient with inspection. The patient's use of support devices such as a cane or walker, the ability to stand up comfortably from a sitting or lying position without assistance should be considered during inspection. All extremities of the patients should be evaluated. Swelling, redness, pallor, coldness, dislocation, anomaly status and pulses in bilateral extremities should be evaluated. If there is unilateral edema and redness, it raises suspicion in terms of deep vein thrombosis. Arterial occlusion may be considered if there is no pulse, coldness, pallor, or numbness. Diabetic geriatric patients, lower extremity examination is important for diabetic foot. Distal interphalangeal nodule (heberden), proximal interphalangeal nodule (bouchard) cause us to think of osteoarthritis (19).

Mental Status

Two assessment tests are most commonly used for mental status assessment in geriatric patients. While applying the "Folstein Mini Mental State Assessment Test", the patient is asked about the date and place. In addition, the patient is shown an object and asked what its name is. Three object names are said and patient is expected to repeat this words and then remember them.It is counted by decreasing 7 from 100.The patient's compliance with verbal and written orders is evaluated.

The sentence is repeated orally and is expected to write a sentence.The patient is instructed to draw two pentagons that intersect with each other. According to the scoring with these parameters, a patient who scores between 24 and 30 is considered to have no cognitive impairment. Patients with a score of 19-23 mild, 10-18 moderate, and 9 and below are considered to have severe cognitive impairment (20).

The mini-cog test, on the other hand, is an assessment test that can be applied more easily than the Folstein test. First, the patient is told three words and expected to remember them. Then patient is asked to draw a clock. Scoring is pretty simple. If patient does not remember any of the three words, or remembers one or two of the three words and draws an abnormal clock, there is a high probability of cognitive impairment. Cognitive impairment is unlikely if the patient remembers three words or remembers one or two of the three words and draws a normal clock (21).

Neurological Examination

Neurological examination is very important in geriatric patients infact, it is necessary to allocate a longer time compared to younger patients. To assess motor functions, the patient is asked to walk. The length, rhythm, speed, walking posture and coordination of the steps are evaluated. In addition, the "Get Up and Go" test is applied to the patient. In this test, the patient is lifted from the chair, walks 3 meters, and is asked to return and sit back in the chair. Further evaluation is required if this test takes more than 15 seconds (22).

"Romberg Test" is done to provide postural balance. In this test, the patient is kept upright with patient’s arms clinging to her body. He is told to close his eyes. Loss of balance after closing the eyes is a sign of disease related to the vestibular system. . Loss of balance with eyes open indicates pathology in the cerebellar system.

While evaluating muscle strength, elderly people may have physiological weakness. If this weakness is symmetrical and does not interfere with the patient's activities, it is considered physiological. Achilles tendon reflex is impaired in most of the elderly, and its asymmetry suggests that it is pathological. Deep tendon reflexes do not

change. Sensory examination is performed in both lower and upper extremities. Light touch, needle touch, heat and vibration are tested. There is no significant change in the sense of touch, but the lower extremity vibration sense decreases (23).

Skin Examination

As a natural result of aging, collagen, elastin fiber degeneration and epidermal atrophy occur. While subcutaneous adipose tissue decreases, vascular fragility increases. After these physiological changes, it is normal for the skin to dry, thin and decrease in turgor. Skin cancers should be evaluated, premalignant and potentially malignant lesions should be evaluated. Bedridden elderly should be evaluated for tissue ischemia and decubitus ulcers (16).

REFERENCES

1. World Health Organization. Ageing and Health, 2022. Access Link: https://www.who.int/news-room/fact-sheets/detail/ageing-and-health [Access Date: 17.10.2022]
2. https://data.tuik.gov.tr/Bulten/Index?p=Istatistiklerle-Yaslilar-2021-45636#:~:text=Ya%C5%9Fl%C4%B1%20n%C3%BCfus%20olarak%20kabul%20edilen,245%20bin%20124%20ki%C5%9Fi%20oldu. (11.10.2022)
3. Medical Clinics of North America, Volume 83, Issue 6, 1 November 1999, Pages 1503-1523
4. Besdine RW. Clinical approch: An overwiev. In: Cassel CK, Cohen HJ, Larson EB, Meier DE, Resnick NM, Rubenstein LZ, Sorensen LB (eds). Geriatric Medicine, 3rd ed. New York, Springer, 1997: 155-168.
5. Prak I, Soydal T, Bal E et al. Elderly Health. T.R. Ministry of Health, General Directorate of Basic Health Services. Pelin Ofset, Ankara. 2002; 67-71.
6. Arslan Ş, Atalay A, Gökçe-Kutsal Y. Yaşlılarda ilaç tüketimi. Turkish Journal Of Geriatrics. 2000; 3: 56-60.
7. https://www.researchgate.net/profile/Veena-Benakatti/publication/329707370_Nutritional_considerations_in_geriatrics/links/5c177622299bf139c75e8777/Nutritional-considerations-in-geriatrics.pdf?_sg%5B0%5D=started_experiment_milestone&origin=journalDetail (14.11.2022)
8. Mathias S, Nayak USL, Isaacs B. Balance in elderly patients: the "get-up and go" test. Arch Phys Med Rehab 1986; 76:387-389.
9. Karan MA. Principles of evaluation of the elderly patient. Current Journal of Medicine 2004; 9:4-8.
10. Besdine RW. Clinical approch: An overwiev. In: Cassel CK, Cohen HJ, Larson EB, Meier DE, Resnick NM, Rubenstein LZ, Sorensen LB (eds). Geriatric Medicine, 3rd ed. New York, Springer, 1997: 155-168.
11. Comprehensive geriatric assessment Savaş S Akçiçek F Ege University, Faculty of Medicine
12. Is There a Relationship Between Malnutrition and Orthostatic Hypotension in Elderly Individuals? Koçyiğit S E, Soysal P, Dokuzlar Ö, Koç Okudur S. Dokuz Eylül University Department

of Geriatrics, İzmir, Turkey Kayseri Training and Research Hospital, Geriatrics Center, Kayseri, Turkey
13. Raiha I, Luuntonen S, Piha J, et al. Prevalance, predisposing factors and prognostic importance of postural hypotension. Arch Intern Med 1995; 155:930-35.
14. Jugular Venous Fullness, Edema, Ascites Prof.Dr.Seçkin Pehlivanoğlu
15. Beers M, Berkow R, eds. In: The Merck Manual of Geriatrics. 3rd ed. USA: Merck & Co. Inc, 2000: 24-40.
16. Edmund HD. Free Medical Textbook. Chapter 1. History and Physical Examination. September 27, 2010. http://medtextfree. wordpress.com
17. Otto CM, Lind BK, Kitzman DW, Gersh BJ, Siscovick DS. Association of aortic-valve sclerosis with cardiovascular mortality and morbidity in the elderly. N Engl J Med 1999;341:142–7.
18. U.S. Preventive Services Task Force: Screening for abdominal aortic aneurysm: recommendation statement. Ann Intern Med 2005; 142:198-202
19. Revascularization of amputation candidate diabetic feet. Uzun A, Diken E, Hanedan O, Çiçek Ö F, Yalçınkaya A, Özsoy H, Taşoğlu İ, Lafçı G. Turkish Journal of Thoracic and Cardiovascular Surgery, 21.4.
20. Folstein MF, Folstein JE, McHugh PR. "Mini Mental State" A practical method for grading the cognitive state of patients fort the clinician. J Psychatr Res 1975; 12:189-198.
21. Borson S, Scanlan JM, Chen P, Ganguli M. The Mini-Cog as a screen for dementia; validation in a population-based sample. J Am Geriatr Soc 2003; 51:1451-4.
22. Mathias S, Nayak USL, Isaacs B. Balance in elderly patients: the "get-up and go" test. Arch Phys Med Rehab 1986; 76:387-389.
23. Romberg Test Jessica Forbes 1, Heather Cronovich 2StatPearls [Internet]. Treasure Island (FL): StatPearls Yayıncılık; 2022 Ocak 2022 Temmuz 29.

CHAPTER 16

EMERGENCY APPROACH TO SALICYLATE AND NON STEROIDAL ANTI-INFLAMMATORY DRUG POISONING

Assoc. Prof. Dr. Emre GÖKÇEN[1]

[1] Yozgat Bozok University, Faculty of Medicine, Department of Emergency Medicine, Yozgat, Türkiye. emregokcenacl@gmail.com, Orcid ID: 0000-0002-6018-6105

1. SALICYLATE

1.1 Introduction

Acetylsalicylic acid, which has analgesic, anti-inflammatory, and anticoagulant effects, is commonly used with and without a prescription. Aspirin is one of the products that contain salcilate. There are also topical salcilates, pain-relieving balms and bismuth combination products. Inappropriate dosage or use for suicidal purposes can lead to toxicity. Once the toxicity situation is identified, prompt and aggressive treatment improves survival (Brubacher & Hoffman, 1996; Halani & Wu, 2020; Toxicology, 2015).

1.2 Pathophysiology

In general, a notable increase in serum concentrations is observed, typically 30 minutes after ingestion of the therapeutic dose, with peak serum levels being reached between 2 and 4 hours (Juurlink et al., 2015). Large intake slows gastric emptying. Enteric-coated preparations in particular tend to form bezoars in the stomach and exhibit irregular absorption (Taylor, Streetman, & Castle, 1998). Situations with similar characteristics can result in prolonged absorption times. This condition is usually associated with elevated serum levels for 12 hours or more. Methyl salicylate or other liquid formulations can provide much faster absorption. Therefore, the serum level can quickly reach peak values (Drummond, Kadri, & St-Cyr, 2001; Rose, Cumpston, Kim, Difranco, & Wills, 2016).

After reabsorption in the liver and blood, aspirin is metabolized to salicylic acid. It then spreads to all body tissues and fluids. Salcilate is the molecule responsible for the therapeutic and toxic effects. Salcilate shows 50-80% binding to plasma proteins. Salcilate is an acidic substance and exists in most ionized forms at physiological pH. Systemic acidemia increases the nonionic fraction of salcilate in the blood. The unnionized fraction can cross the blood-brain barrier and increase cerebral salicylic acid levels (Pearlman & Gambhir, 2009; Toxicology, 2015).

Respiratory alkalosis, tachypnea, and hyperpnea develop as a result of salcilate stimulating the medullary respiratory center. As toxicity develops, inhibition of metabolism deepens acidosis. In general, the acid-base disturbance in salcilate poisoning is of the mixed type. Respiratory alkalosis occurs in the early stages. Later, metabolic acidosis develops with an increased anion gap

and later respiratory acidosis. The coexistence of respiratory alkalosis and metabolic acidosis leads to confusion with sepsis syndromes. When ingested toxically, ingestion along with central nervous system depressants may suppress initial respiratory stimulation. Salcilate can stimulate skeletal muscle metabolism towards oxygen consumption and carbon dioxide production. Neurological toxicity can impair the patient's respiratory response, leading to carbon dioxide retention and respiratory acidosis (Juurlink et al., 2015; Patel et al., 1990).

Glucose metabolism can also be influenced by salcilate. Although salcilate is a potent inhibitor of gluconeogenesis, it can lead to hyperglycemia by depleting glycogen stores. Therefore, although normoglycemia is generally noted, hyperglycemia is occasionally observed. Hypoglycemia is rare (Lim, Marcelo, & Bryant, 2016).

Salcilates cause symptoms such as abdominal pain, nausea and vomiting as a result of damage to the gastrointestinal tract with their caustic effect. It can be seen occasionally depending on the extent of the hematemesis. There are even cases of gastric perforation (Robins, Turnbull, & Robertson, 1985). Non-cardiogenic pulmonary edema may occur. Platelet aggregation inhibition can lead to bleeding. Excessive intake can lead to hypoprothrombinemia due to inhibition of vitamin K-dependent functions (Hatten & Hendrickson, 2019).

Salcilate ototoxicity is common, tinnitus can occur at around 20 mg/dl. Some patients may describe deafness and blurred hearing. Hearing damage is not permanent and the exact mechanisms are still unclear.

1.3 Clinical Features

The severity of salcilate toxicity is determined by the dose taken, the time of exposure, the patient's age and comorbidities. More severe symptoms may occur in the elderly and children even at lower serum salcilate levels. Chronic toxicity may not correlate with the amount of drug ingested and serum salcilate levels. In these cases, a severe clinical course or a gradual course cannot be predicted (Pearlman & Gambhir, 2009; Toxicology, 2015).

Intoxication due to chronic or recurrent ingestion of salcilate at therapeutic doses in children is generally clinically more severe. Salcilate poisoning in children develops several days after acute ingestion. Administration of salcilates, usually due to a concomitant disease, causes a

more severe clinical response due to normal toxicity. The clinical picture in children is usually associated with fever, altered mental status, hyperventilation, metabolic acidosis, and severe hypokalemia. Hyperpyrexia is a sign of poor prognosis. Although kidney failure is common in children with salcilate poisoning, lung damage is rare. Taking prescription or family-administered salcilate should be a warning to the doctor (Gaudreault, Temple, & Lovejoy Jr, 1982; Snodgrass, Rumack, Peterson, & Holbrook, 1981).

Suicidal ingestion is usually the underlying cause of salcilate poisoning in adults. Nausea, vomiting, hearing loss, and tinnitus are the usual clinical findings (Dargan, Wallace, & Jones, 2002; Pearlman & Gambhir, 2009). Hyperventilation is a common finding. Salcilate-induced non-cardiogenic pulmonary edema can be observed (Thongprayoon et al., 2020; Yuklyaeva, Chaudhary, Gorantla, & Bischof, 2014). This is due to increased pulmonary vascular permeability. In severe poisoning, sudden cardiac arrest may occur due to respiratory depression. Mixed type acid-base disorders are observed in adults with salcilate intoxication. Altered mental status levels can be detected in patients when central nervous system toxicity develops. Clinical findings such as restlessness, seizures and coma can be seen across a wide spectrum. Although serum salcilate levels are reduced by treatment, progressive neurologic deterioration may be due to central salcilate levels crossing the brain barrier. Due to the irritating effect of the drug, conditions such as gastric bleeding may occur. Caution should also be exercised with regard to gastric perforation. Excessive vomiting can lead to volume depletion and metabolic alkalosis. this can lead to decreased renal blood flow and urinary excretion. In addition, high levels of salcilate can decrease renal blood flow and glomerular filtration rate due to inhibition of prostaglandin synthesis. As a result of the resulting kidney damage, water and salt deposits occur in the body. Especially in elderly patients, caution is required with regard to renal insufficiency (Dargan et al., 2002; Pearlman & Gambhir, 2009; Thongprayoon et al., 2020; Toxicology, 2015).

Chronic salcilate poisoning can be observed in elderly people due to overdose with repeated intake. In general, neurological symptoms predominate. An altered state of mind is observed in a wide area. The general findings of chronic poisoning are hyperventilation, tremors, inappropriate behavior patterns, agitation, memory loss and confusion. Nausea and vomiting are rarer

findings in chronic poisoning. A mixed acid-base disorder and unexplained neuropsychiatric symptoms should indicate chronic salcilate intoxication in the elderly (Palmer & Clegg, 2020; Pearlman & Gambhir, 2009; Petnak et al., 2021).

1.4. Diagnosis

In the case of salcilate poisoning, in addition to the laboratory findings, it is important to determine the serum salcilate concentration, the serum potassium and the glucose level. The acid-base status is an important indicator. The Done nomogram, historically used for salcilate toxicity, is no longer used to monitor the prognosis and management of the disease. The trick to measuring serum salcilate levels is not to stick with a single level measurement. Situations where salcilates were not detected in the first hours after taking salcilate have occurred. In the case of salcilate toxicity, it may be useful to measure the serum salcilate concentration every two hours until the patient's clinical condition has stabilized. Commercially available matches that measure cerusalcilate levels are generally accurate. In patients taking Diflunisal, a concomitant non-steroidal anti-inflammatory drug, a false positive measurement is observed in the measurement of serum salcilate. The therapeutic dose range of salcilate levels varies between 150-300 mcg/ml (Palmer & Clegg, 2020; Shively, Hoffman, & Manini, 2017; Szucs, Shih, Marcus, Leff, & Delgado, 2000; Toxicology, 2015).

1.5. Treatment

There is no specific antideath treatment for salcilate poisoning. The primary goals of treatment can be listed as follows (Dargan et al., 2002; O'Malley, 2007).

1. Basic and advanced life support, emergency resuscitation;
2. Correction of volume depletion and metabolic disorders;
3. gastrointestinal decontamination;
4. Reducing the salicylate load in the body.

Accurate determination of vital signs in salcilate poisoning is the first step in assessment. Chest auscultation may provide evidence of pulmonary edema, and altered mental status may indicate central nervous system toxicity. Due to the hypermetabolic state, dehydration occurs early in salicylate

intoxication, and initial fluid requirements can be as high as 4 to 6 L. Fluid intake should be based on the patient's apparent deficit to maintain a urinary output of 2 to 3 mL/kg/h. It is important to avoid potassium consumption in order to keep serum levels between 4.5 and 5.0 mEq/L (4.5-5.0 mmol/L) (Palmer & Clegg, 2020; Petnak et al., 2021; Toxicology, 2015).

Urinary alkalinization is important to ensure urinary excretion of salcilate. Initial fluid therapy and urine alkalinization can be performed simultaneously if needed. Urinary salicylate clearance is directly proportional to urine flow rate, but more importantly, it is logarithmically proportional to urine pH. Urinary alkalinization is more effective than forced diuresis in increasing salicylate excretion. It prevents the administration of large amounts of intravenous fluids to increase urine volume. Thus, potential complications of fluid overload are avoided. After a bolus of 1-2 mEq/kg via a second intravenous line, three vials of sodium bicarbonate in 5% dextrose are given and infused. The infusion rate is adjusted so that the urine pH is above 7.5. The aim should be to maintain urine pH in the range of 7.5-8.5 and not to raise blood pH above 7.55. The development of pulmonary edema due to fluid overload is an undesirable complication (Givertz, 2020; Pearlman & Gambhir, 2009; Toxicology, 2015).

The clinical follow-up of the patient should be carefully performed. The patient's urine pH, volume status, metabolic values, serum salcilate concentration should be monitored frequently. Cariopulmonary and neurological status should be considered. Hemodialysis should be strongly considered when treating severe salcilate poisoning. The decision to start hemodialysis should not be based solely on serum salcilate levels. Findings such as renal failure, severe acid-base imbalance, altered mental status, and pulmonary edema associated with salcilate levels should guide the clinician (Pearlman & Gambhir, 2009; Toxicology, 2015).

1.6. Discharge

Neurologically, cardiopulmonary and metabolically affected patients should be followed up in the intensive care unit. Intentionally suicidal purchases should be considered and a psychiatrist's opinion sought. Elderly and pediatric patients as well as patients with suspected chronic poisoning should be hospitalized. Early consultation with a clinical toxicologist or regional

poison control center is recommended (Pearlman & Gambhir, 2009; Toxicology, 2015).

2. NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

2.1. Introduction

Non-Steroidal Anti-Inflammatory Drugs (NSAIDS) are among the drugs known to be used extensively around the world. Inhibition of prostaglandin as a result of inhibition of the cyclooxygenase enzyme is a common mechanism of action (Jones, 2002; Volans, Hartley, McCrea, & Monaghan, 2003).

Nonsteroidal anti-inflammatory drugs have anti-inflammatory and antipyretic effects. Nonsteroidal anti-inflammatory drugs are almost completely absorbed from the upper small intestine. NSAIDs have a low volume of distribution due to their high plasma protein binding. Hepatic biotransformation plays an important role in elimination (Al-Abri, Anderson, Pedram, Colby, & Olson, 2015).

2.2. Pharmacology-Pharmacokinetics

NSAIDs are compounds that may differ structurally but share therapeutic effects. NSAIDs work by reversibly inhibiting COX, which is responsible for the production of prostaglandins. The anti-inflammatory effect of NSAIDs is manifested by inhibition of prostaglandin production and neutrophil migration. NSAIDs lower body temperature by inhibiting prostaglandin E2 in the hypothalamus. Its analgesic effects occur through down-regulation of prostaglandin-mediated hyperalgesia and local pain fiber stimulation. COX has two isoforms, COX-1 and COX-2. COX-1 is mainly found in blood vessels, kidneys and stomach, while COX-2 is found in low amounts in human tissues. . COX-1 inhibition has been linked to many of the undesirable GI side effects of NSAIDs. Although COX-2 selective compounds have been made to avoid these side effects, they still appear to be responsible for GIS side effects (Bertolotto et al., 2014; Brune & Patrignani, 2015; Meirer, Steinhilber, Proschak, pharmacology, & toxicology, 2014; Moore, Derry, Phillips, & McQuay, 2006).

2.3. Clinical Features

NSAIDs are relatively safe drugs with known side effects at therapeutic doses. With acute intoxication and chronic ingestion, morbidity is associated with gastrointestinal bleeding and renal failure. In therapeutic doses, symptoms of intoxication can be observed in the central nervous system, respiratory system, cardiovascular system, liver and skin (Al-Abri et al., 2015; Auriel, Regev, & Korczyn, 2014; Patrono & Baigent, 2014).

Studies have shown that NSAIDs have more gastrointestinal side effects. The risk group is particularly high in people who are elderly, have stomach ulcers and have taken high doses in the past. NSAIDs can cause epithelial damage, superficial petechiae, and occult and massive bleeding with direct attachment to the gastric and duodenal mucosa (Al-Abri et al., 2015; Moore et al., 2006).

In patients with hypovolaemia and concomitant hypotension, NSAID overdose has been associated with renal dysfunction. NSAIDs can cause kidney failure by inhibiting the synthesis of vasodilator prostaglandins, leading to a decrease in renal blood flow and glomerular filtration rate. They also increase potassium reuptake by lowering renin levels and decreasing sodium reabsorption in the distal tubule. In this way, they can lead to hyperkalemia (Cabassi et al., 2020; Harirforoosh, Asghar, Jamali, & Sciences, 2013).

NSAIDs can cause central nervous system symptoms such as headache, dizziness, depression, confusion, hallucinations and tinnitus. These side effects are more common in older people and at higher doses. A rare side effect of NSAIDs is aseptic meningitis. Cases reported symptoms such as fever, stiff neck and headaches occurring within a few hours of taking the drug (Auriel et al., 2014; Holle, Obermann, & Reports, 2015; Moreno-Ancillo, Gil-Adrados, Jurado-Palomo, & Immunology, 2011).

NSAIDs can cause bronchospasm by inhibiting the synthesis of bronchodilator prostaglandins. They can lead to findings such as hypersensitivity pneumonia and pulmonary edema (Morales et al., 2015). NSAIDs inhibit platelet aggregation by inhibiting tomboxan A2 and prolong bleeding time. Side effects such as aplastic anemia, thrombocytopenia, agranulocytosis, hemolytic anemia can be observed (Benmoussa, Chevenon, Nandi, Forlenza, & Nfonoyim, 2016; Oregel, Ramdial, & Glück, 2013).

2.4. Treatment

It has been reported that most acute overdose patients are asymptomatic at the time of admission to the emergency department. Symptomatic patients should be managed according to the principles of emergency medicine and toxicology. Treatment for NSAID overdose is largely supportive and there is no specific antidote. Activated charcoal can be tried in patients with an intact mental state and NSAID overdose that protects their airways. IV fluids and an H2 blocker or proton pump inhibitor can be administered empirically. Patients with symptomatic NSAID overdose should have a serum chemistry panel, liver profile, complete blood count, and coagulation profile. NSAID serum levels do not correlate with observed toxicity or results, therefore serum levels for specific NSAIDs are not reported. Symptomatic patients with altered mental status, seizures, shock, dyspnoea, or cardiac arrhythmias require aggressive resuscitation and stabilization. NSAIDs are highly protein bound. Similarly, manipulation of serum and urine pH by intravenous alkalinization is not beneficial to increase renal excretion. Severe metabolic disorders or renal failure unresponsive to conservative treatments may require hemodialysis (Cappell & Schein, 2000; Hunter, Wood, & Dargan, 2011; Saad & Mathew, 2018; Sandilands & Bateman, 2016).

2.5. Discharge

Hemodynamically stable patients should be reevaluated with a history and complete physical examination. Asymptomatic patients may be discharged to the emergency department on recommendation after a follow-up period of 4-6 hours if they are not taking any other medications concomitantly. Patients with symptoms (acute renal failure, mental status change, electrolyte abnormalities, abnormal vital signs, etc.) should be hospitalized for observation and supportive care. All overdoses should be reported to regional poison control agencies to aid in treatment management and to raise awareness.

REFERENCES

Al-Abri, S. A., Anderson, I. B., Pedram, F., Colby, J. M., & Olson, K. R. (2015). Massive naproxen overdose with serial serum levels. Journal of Medical Toxicology, 11(1), 102-105.

Auriel, E., Regev, K., & Korczyn, A. D. (2014). Nonsteroidal anti-inflammatory drugs exposure and the central nervous system. Handbook of clinical neurology, 119, 577-584.

Benmoussa, J., Chevenon, M., Nandi, M., Forlenza, T. J., & Nfonoyim, J. (2016). Ibuprofen-induced thrombotic thrombocytopenic purpura. The American Journal of Emergency Medicine, 34(5), 942-e5.

Bertolotto, M., Contini, P., Ottonello, L., Pende, A., Dallegri, F., & Montecucco, F. (2014). Neutrophil migration towards C 5a and CXCL 8 is prevented by non-steroidal anti-inflammatory drugs via inhibition of different pathways. British Journal of Pharmacology, 171(14), 3376-3393.

Brubacher, J. R., & Hoffman, R. S. (1996). Salicylism from topical salicylates: review of the literature. Journal of Toxicology: Clinical Toxicology, 34(4), 431-436.

Brune, K., & Patrignani, P. (2015). New insights into the use of currently available non-steroidal anti-inflammatory drugs. Journal of pain research, 8, 105.

Cabassi, A., Tedeschi, S., Perlini, S., Verzicco, I., Volpi, R., Gonzi, G., & Canale, S. D. (2020). Non-steroidal anti-inflammatory drug effects on renal and cardiovascular function: from physiology to clinical practice. European journal of preventive cardiology, 27(8), 850-867.

Dargan, P. I., Wallace, C. I., & Jones, A. L. (2002). An evidence based flowchart to guide the management of acute salicylate (aspirin) overdose. Emergency Medicine Journal, 19(3), 206-209.

Drummond, R., Kadri, N., & St-Cyr, J. (2001). Delayed salicylate toxicity following enteric-coated acetylsalicylic acid overdose: a case report and review of the literature. Canadian Journal of Emergency Medicine, 3(1), 44-46.

Gaudreault, P., Temple, A. R., & Lovejoy Jr, F. H. (1982). The relative severity of acute versus chronic salicylate poisoning in children: a clinical comparison. Pediatrics, 70(4), 566-569.

Givertz, M. M. (2020). Noncardiogenic pulmonary edema. UpTo-Date, T. Post, Ed., UpToDate, Waltham, MA.

Halani, S., & Wu, P. E. (2020). Salicylate toxicity from chronic bismuth subsalicylate use. BMJ Case Reports CP, 13(11), e236929.

Harirforoosh, S., Asghar, W., & Jamali, F. (2013). Adverse effects of nonsteroidal antiinflammatory drugs: an update of gastrointestinal,

cardiovascular and renal complications. Journal of Pharmacy & Pharmaceutical Sciences, 16(5), 821-847.

Hatten, B. W., & Hendrickson, R. G. (2019). Reply to'In response to'Coagulopathy and bleeding associated with salicylate toxicity"". Clinical Toxicology (Philadelphia, Pa.), 58(5), 432-433.

Dagny, H., & Obermann, M. (2015). Headache in Drug-Induced Aseptic Meningitis. Current Pain and Headache Reports, 19(7).

Hunter, L. J., Wood, D. M., & Dargan, P. I. (2011). The patterns of toxicity and management of acute nonsteroidal anti-inflammatory drug (NSAID) overdose. Open access emergency medicine: OAEM, 3, 39.

Jones, A. (2002). Over-the-counter analgesics: a toxicologic perspective. American journal of therapeutics, 9(3), 245-257.

Juurlink, D. N., Gosselin, S., Kielstein, J. T., Ghannoum, M., Lavergne, V., Nolin, T. D., ... & Yates, C. (2015). Extracorporeal treatment for salicylate poisoning: systematic review and recommendations from the EXTRIP workgroup. Annals of emergency medicine, 66(2), 165-181.

Lim, C. S., Marcelo, C. B., & Bryant, S. M. (2016). Those Salicylate Cases—How Sweet Are They?. American Journal of Therapeutics, 23(5), e1155-e1156.

Meirer, K., Steinhilber, D., & Proschak, E. (2014). Inhibitors of the arachidonic acid cascade: interfering with multiple pathways. Basic & clinical pharmacology & toxicology, 114(1), 83-91.

Moore, R. A., Derry, S., Phillips, C. J., & McQuay, H. J. (2006). Nonsteroidal anti-inflammatory drugs (NSAIDs), cyxlooxygenase-2 selective inhibitors (coxibs) and gastrointestinal harm: review of clinical trials and clinical practice. BMC musculoskeletal disorders, 7(1), 1-13.

Morales, D. R., Guthrie, B., Lipworth, B. J., Jackson, C., Donnan, P. T., & Santiago, V. H. (2015). NSAID-exacerbated respiratory disease: a meta-analysis evaluating prevalence, mean provocative dose of aspirin and increased asthma morbidity. Allergy, 70(7), 828-835.

Moreno-Ancillo, A., Gil-Adrados, A. C., & Jurado-Palomo, J. (2011). 8 Ibuprofen-Induced Aseptic Meningoencephalitis Confirmed by Drug Challenge. Journal of Investigational Allergology and Clinical Immunology, 21(6), 484.

O'Malley, G. F. (2007). Emergency department management of the salicylate-poisoned patient. Emergency medicine clinics of North America, 25(2), 333-346.

Oregel, K. Z., Ramdial, J., & Glück, S. (2013). Nonsteroidal anti-inflammatory drug induced thrombotic thrombocytopenic purpura. Clinical Medicine Insights: Blood Disorders, 6, CMBD-S12843.

Palmer, B. F., & Clegg, D. J. (2020). Salicylate Toxicity. The New England journal of medicine, 382(26), 2544–2555.

Patel, D. K., Hesse, A., Ogunbona, A., Notarianni, L. J., & Bennett, P. N. (1990). Metabolism of aspirin after therapeutic and toxic doses. Human & experimental toxicology, 9(3), 131-136.

Patrono, C., & Baigent, C. (2014). Nonsteroidal anti-inflammatory drugs and the heart. Circulation, 129(8), 907-916.

Pearlman, B. L., & Gambhir, R. (2009). Salicylate intoxication: a clinical review. Postgraduate medicine, 121(4), 162-168.

Petnak, T., Thongprayoon, C., Kaewput, W., Qureshi, F., Boonpheng, B., Vallabhajosyula, S., ... & Cheungpasitporn, W. (2021). Circulatory shock among hospitalized patients for salicylate intoxication. Diseases, 9(1), 7.

Robins, J. B., Turnbull, J. A., & Robertson, C. (1985). Gastric perforation after acute aspirin overdose. Human toxicology, 4(5), 527-528.

Rose, S. R., Cumpston, K. L., Kim, J., Difranco, D., & Wills, B. K. (2016). Absorption of salicylate powders versus tablets following overdose: a poison center observational study. Clinical toxicology, 54(9), 857-861.

Saad, J., & Mathew, D. (2018). Nonsteroidal Anti-Inflammatory Drugs Toxicity.

Sandilands, E. A., & Bateman, D. N. (2016). Non-steroidal anti-inflammatory drugs. Medicine, 44(3), 185-186.

Shively, R. M., Hoffman, R. S., & Manini, A. F. (2017). Acute salicylate poisoning: risk factors for severe outcome. Clinical toxicology, 55(3), 175-180.

Snodgrass, W., Rumack, B. H., Peterson, R. G., & Holbrook, M. L. (1981). Salicylate toxicity following therapeutic doses in young children. Clinical Toxicology, 18(3), 247-259.

Szucs, P. A., Shih, R. D., Marcus, S. M., Leff, K., & Delgado, P. (2000). Pseudosalicylate poisoning: falsely elevated salicylate levels in an overdose of diflunisal. The American journal of emergency medicine, 18(5), 641-642.

Taylor, J. R., Streetman, D. S., & Castle, S. S. (1998). Medication bezoars: a literature review and report of a case. Annals of Pharmacotherapy, 32(9), 940-946.

Thongprayoon, C., Petnak, T., Kaewput, W., Mao, M. A., Kovvuru, K., Kanduri, S. R., ... & Cheungpasitporn, W. (2020). Hospitalizations for acute salicylate intoxication in the United States. Journal of clinical medicine, 9(8), 2638.

American College of Medical Toxicology jmt@ acmt. net. (2015). Guidance document: management priorities in salicylate toxicity. Journal of Medical Toxicology, 11(1), 149-152.

Volans, G., Hartley, V., McCrea, S., & Monaghan, J. (2003). Non-opioid analgesic poisoning. Clinical medicine, 3(2), 119.

Yuklyaeva, N., Chaudhary, A., Gorantla, R., & Bischof, E. (2014). Salicylate-induced pulmonary edema—a near-miss diagnosis. The American Journal of Emergency Medicine, 32(5), 490-e5.

CHAPTER 17

HYPNOSIS IN EMERGENCY DEPARTMENT

Assoc. Prof. Dr. Harun GUNES[1]

[1] Balikesir University, School of Medicine, Department of Emergency Medicine, Balikesir, Turkey. haroonsun@hotmail.com, Orcid ID: 0000-0003-4899-828X

INTRODUCTION

Hypnosis can be defined as an altered state of consciousness which uses focused concentration, imagination, and restriction of perception to affect changes in sensation, perception, and physiology (Peebles-Kleiger, 2000, p. 327). Although the word hypnosis is derived from the Greek “hypnos”, which means sleep, it is actually a state of highly focused awareness. It is an altered, but not decreased, state of consciousness during which an individual is able to have an elevated control over sensory modalities through suggestion and imagination. Practitioner, who performs hypnosis, does not control the patient but guides the patient’s ability to control his or her own sensory state (Güneş & Koyuncu, 2021, p. 25).

Hypnosis can be used as a valuable adjunct to patient management in the emergency department (ED) setting. Its possible applications include, but not limited to, pain management, sedation, pediatric procedures, surgery, burns, and certain psychiatric and obstetric presentations (Peebles-Kleiger, 2000, p. 327). It can also be easily used in the pre-hospital setting (Iserson, 2014, p. 588). However, there are some myths about hypnosis which have interfered with its use in emergency medicine (EM). These are mostly about the hypnotist – can totally control the patient; can learn all secrets of the patient etc. –, the length of induction time (too long to be used in the emergency setting), and the traumatized patient's inability to concentrate on a focal point. It is suggested, however, that altered states of awareness occur rapidly and spontaneously in the patient who has experienced acute trauma and/or pain recently (Wain & Amen, 1986, p. 19). And, applications of hypnosis in the ED are mostly related to traumatic (physical or emotional) and painful conditions so one can say most of the patients who are candidates for hypnosis application in the ED are nearly ready to enter hypnotic state. Goldie (1956) stated that “The impression was gained that some of the most anxious children were the most easily induced”. Besides, hypnosis fulfills nearly all requirements of the ideal ED intervention; a safe, fast, readily available and cost-effective tool which uses minimal personnel and equipment, and has no risks like infection, prolonged sedation or other risks associated with sedation or medication administration. The use of hypnosis, instead of or in combination with drugs, for purposes of sedation and analgesia will be particularly more beneficial in the case of pregnancy, liver or renal

insufficiency (seen in a considerable proportion of the elderly), or history of drug allergy or abuse. (Güneş & Koyuncu, 2021, p. 25).

1. A Short History of Hypnosis

Hypnosis was used for religious and medical purposes at least 4000 years ago in Egypt, and the ancient Greeks also used it in ‘‘sleep temples of the sick.’’ Use of hypnosis in modern medicine began in 1778; Austrian physician Franz Anton Mesmer introduced it in France (Iserson, 2014, p. 589). Jules Cloquet (mastectomy operations) and John Elliotson (various different operations) performed lots of major surgical procedures using hypnosis as the only anesthetic in the early 19th century. The Scottish physician James Esdaile used hypnosis in nearly 300 surgical patients in India between 1845 and 1851. However, chemical anesthetics (ether 1846, chloroform 1847) were introduced into surgical practice almost simultaneous with Esdaile's report, and hypnosis subsequently lost its popularity as a therapeutic tool (Wobst, 2007, p. 1199). In the early 20th century, and of particular relevance to EM, P. P. Podiapolsky who was a physician and a psychotherapist saw that nearly all wounded soldiers greatly responded to hypnosis (Iserson, 2014, p. 589). Then, hypnosis was endorsed as a technique in 1955 by the British Medical Society and in 1958 by the American Medical Association (Rogovik & Goldman, 2007, p. 823). Finally, İn 1996, an NIH Technology Assessment Panel confirmed hypnosis as an effective adjunct in alleviating pain (Peebles-Kleiger, 2000, p. 327).

2. Potential Areas of the Use of Hypnosis in the Emergency Department

Clinical conditions in which hypnosis can be used in ED grossly fall into two categories namely “management of pain” and “sedation and anxiolysis”. Actually, these two clinical scenarios may accompany each other in a single patient. However, they are going to be discussed separately to emphasize some significant issues related to each one.

2.1. Management of Pain

The ED, where painful medical problems and patients in fear are frequently treated and several painful procedures are performed, represents

one area in which hypnosis can be considered (Iserson, 1999, p. 53). Painful conditions where hypnosis can be used in ED include providing analgesia for existing pain (e.g. fractures, burns, lacerations, renal colic, myocardial infarction etc.) and providing analgesia for painful procedures and interventions (e.g. needle sticks, laceration repair, foreign body removal, incision and drainage, fracture and joint reductions, some obstetric/gynecologic examinations and interventions like embryo transfer) (Güneş & Koyuncu, 2021, p. 26). Scans show that pain under hypnosis is not perceived, rather than simply being experienced with greater tolerance (Iserson, 2014, p. 589). The analgesic effect of hypnosis is not solely a placebo effect which can suppress pain in approximately 20 to 30% of patients. Placebo appears to be effective through the endogenous opiate system and can be blocked by naloxone; hypnosis is a modulator of pain and its effect is not blocked by naloxone (Deltito, 1984, 265). Neurophysiologic studies show that hypnosis differs from simple imagination, placebo, and sleep (Dumont, Martin & Broer, 2012, p. 61). Positron emission tomography (PET) studies demonstrates that the effect of hypnosis involves the anterior cingulate cortex, and the brain's perception actually changes; this is not observed when a suggestible person simply follows instructions (Kosslyn, Thompson, Costantini-Ferrando, Alpert & Spiegel, 2000, p. 1282). PET also shows that hypnosis modulates a large cortical network through the mid-cingulate cortex and actively decreases subjective and objective perception of pain (Iserson, 2014, p. 589; Faymonville et al., 2003, p. 255). So, it has been proven that hypnosis is a really effective tool even in the management of pain with organic origin. However, ED patients and their relatives were seen to be reluctant to prefer hypnosis except in the existence or possibility of drug dependence. It was seen that mostly the accumulation of common misleading information in the patients' and their relatives' mind is responsible for this. The most common sources of that misleading information are television, movies, rumors and stage hypnosis shows. Therefore, it was suggested that, before starting to think about using hypnosis techniques in patients suffering from pain in ED, the population should be educated on hypnosis so that people can get rid of common myths and misconceptions about hypnosis (Güneş & Koyuncu, 2021, p. 33).

2.2. Sedation and Anxiolysis

A possible application area of hypnosis in ED is patients needing sedation and anxiolysis. Patients may require sedation in ED due to several reasons including painful clinical conditions, which was discussed above; some procedural interventions like a needle stick to draw blood sample or insert a peripheral intra-venous line in a child, needle phobia in an adult, suturing a laceration, avulsion of a nail, insertion of a nasogastric tube, a urinary catheter or a central venous catheter; fracture or joint reduction; anxiety related to a psychological problem other than psychoses or a recent traumatic incident (physical or emotional); some physical examinations like gynecologic examination especially in a young patient like a teenager or a post-rape examination or even during embryo transfer procedure and so on (Iserson, 1999, p.56; Catoire et al., 2013, p. 385). Hypnosis can be used instead of sedative agents in some of these situations like needle stick in a child, nasogastric or urinary catheter insertion, anxious patients and some physical examinations or in combination with sedative and analgesic medications in the others like laceration repair, central venous catheter insertion (together with local anesthetics) and fracture or joint reduction (together with parenteral analgesics and sedatives). If hypnosis is applied along with sedative and/or analgesic medications it can allow physicians use lower doses of medications to effectively provide adequate sedation and/or analgesia. This is especially important in the case of renal or liver insufficiency or pregnancy because the lesser the dose of medication the lower the risk of possible unwanted effects in these special groups (Iserson, 2014, p. 590; Goldie, 1956, p. 1341). Some advantages of hypnosis over sedative agents are lower cost, need for lesser personnel, lack of adverse effects like prolonged sedation, nausea, vomiting, risk of aspiration and pneumonia, and complications related to parenteral medication administration like infection (Iserson, 1999, p.56).

3. Hypnosis Induction Technique

There are multiple techniques that can be used to induce hypnosis like the arm-drop, arm levitation, bionic arm (for children), association, confusion, two-finger, and direct gaze. One can easily learn basic hypnotic techniques. Many physicians suggest that the following method is extremely easy to learn and use (Iserson, 2014, p. 591). Before starting the induction of hypnosis, in the "pre-induction phase", the practitioner usually describes the process to the patients as "a way to relax", thus misconceptions they might have about hypnosis are not going to interfere with their cooperation. The practitioner should also establish rapport with the patient before proceeding to the next step. A key element, especially in the noisy environment of the ED, is to stress that the patient should listen only to the practitioner, and that the process will proceed at the patient's pace, without any pressure. The practitioner should speak in a firm and quiet manner, and should not react to any of the noisy or distracting activities in the immediate proximity. The practitioner instructs the patient to close the eyes and relax. Then, the patient is asked to concentrate on the distal extremities, to imagine sensation of heaviness in the limbs as "all of the muscles in the toes relax." Approximately 30 to 45 seconds is spent to help patient to concentrate on and relax the toes. After this step is completed, the remainder of the process is easier. Then, the practitioner suggests that the patient feel the heaviness flow up into the feet, then the legs, thighs, etc. At this time, the practitioner instructs the patient to slow the rate of breathing and further allow the entire body to relax. It is really helpful to suggest that another level of relaxation will be attained with each exhalation. Later, the practitioner tells that the patient will feel relaxed, sleepy, and will "travel in the mind to a very pleasant place like a beach or mountain." A suggestion can be made that the patient will not remember the process of, and pain during, the procedure after hypnosis is terminated (Iserson, 1999, p. 54). If hypnosis is induced to decrease pain which is already present, the practitioner can instruct the patient that "he or she feels numbness in that part of the body and doesn't feel that pain any more" (Iserson, 2014, p. 592). The same can also be applied to sedation or anxiolysis. As it was mentioned above, there are many different techniques which can be used to induce hypnosis; only one, which is used in pain management, is briefly described here.

4. Why Hypnosis isn't Used by Emergency Physicians

Most emergency physicians don't use hypnosis in their daily practice although it has been used in modern medicine for more than two centuries (Güneş & Koyuncu, 2021, p. 25). One of the most important barriers to use of hypnosis in modern medicine and also in ED is its association with alternative-complimentary medicine (Iserson, 2014, p. 593). Hypnosis unfortunately is surrounded by some myths and has the stigma of charlatanism due to faults of some of its practitioners. Lack of training and concerns of emergency physicians about reluctance of patients to accept the use of hypnosis are also significant inhibitory factors (Boulton, 1967, p. 105; Güneş & Koyuncu, 2021, p. 26). "Fear of the unknown" is a significant factor preventing more common clinical use of hypnosis in ED. There are very common misconceptions about hypnosis such as "the patient enters total control of the hypnotist"; "some patients cannot terminate hypnosis even if they want to do so"; "the hypnotist can learn all secrets of the patient" and so on. Although none of these assumptions are true, they are commonly believed by general population, and they prevent most people from admitting the physician to use hypnosis as a part of their treatment. Because emergency physicians know this fact, most of them don't try to use and even think using hypnosis in ED. Training of emergency physicians and education of the population about hypnosis can reduce the fear of both sides of the ED use of hypnosis. Before offering hypnosis to the patient as an adjunct or substitute to medical agents, a short explanation about hypnosis, which also includes common misconceptions, some of which are mentioned above, will also significantly help.

5. Conclusion

Hypnosis has been used for medical purposes for thousands of years, and it has also been safely used in modern medicine for more than two centuries. It can be used in ED as an adjunct to sedative and analgesic agents in some situations like liver or renal insufficiency; it can even be a substitute for these medications in some situations such as pregnancy, drug allergy or abuse. Its efficacy has been proven by scientific studies in modern medicine, and it has also been shown hypnosis does not have any significant adverse effects which can prevent emergency physicians from using it in ED.

However, its more common use is inhibited by several factors which are mostly based on myths originating from insufficient knowledge of the general population about hypnosis, and the lack of training of emergency physicians on hypnosis. Therefore, hypnosis can get to the right place in ED with the help of education of the population and training of emergency physicians. When a critical threshold is reached in the use of hypnosis in ED, then it is going to be more and more commonly used day-by-day even by those who stand against its use in ED or modern medicine nowadays.

REFERENCES

Boulton, T.B. (1967, Jan). Anaesthesia in difficult situations. Anaesthesia, 22,101-33. doi: 10.1111/j.1365-2044.1967.tb02699.x.

Catoire, P., Delaunay, L., Dannappel, T., Baracchini, D., Marcadet-Fredet, S., Moreau, O., Pacaud, L., Przyrowski, D., Marret, E. (2013, Apr). Hypnosis versus diazepam for embryo transfer: a randomized controlled study. Am J Clin Hypn, 55(4),378-86. doi: 10.1080/00029157.2012.747949.

Deltito, J.A. (1984, Apr). Hypnosis in the treatment of acute pain in the emergency department setting. Postgrad Med J, 60(702), 263-6. doi: 10.1136/pgmj.60.702.263.

Dumont, L., Martin, C. and Broer, I. (2012). Functional Neuroimaging Studies of Hypnosis and Meditation: A Comparative Perspective. J Mind Body Regul, 1,58-70

Faymonville, M-E., Roediger, L., Del Fiore, G., Delgueldre, C., Phillips, C., Lamy, M., Luxen, A., Maquet, P., Laureys, S. (2003, Jul). Increased cerebral functional connectivity underlying the antinociceptive effects of hypnosis. Brain Res Cogn Brain Res, 2:255-62. doi: 10.1016/s0926-6410(03)00113-7.

Goldie, L. (1956). Hypnosis in the Casualty Department. Br Med J, 2,1340-2. doi: 10.1136/bmj.2.5005.1340.

Güneş, H. and Koyuncu S. (2021). Knowledge Level and Beliefs of Patients and Their Relatives about Hypnosis and Their Attitudes toward Use of Hypnosis for Sedation and Analgesia Purposes in the Emergency Department. Eurasian J Emerg Med, 20(1), 25-34 doi: 10.4274/eajem.galenos.2021.18894

Iserson, K.V. (2014, Apr). An hypnotic suggestion: review of hypnosis for clinical emergency care. J Emerg Med, 46(4), 588-96. doi: 10.1016/j.jemermed.2013.09.024. Epub 2014 Jan 25.

Iserson, K.V. (1999, Jan-Feb). Hypnosis for pediatric fracture reduction. J Emerg Med, 17(1),53-6. doi: 10.1016/s0736-4679(98)00114-0.

Kosslyn, S.M., Thompson, W.L., Costantini-Ferrando, M.F., Alpert, N.M., D Spiegel, D. (2000, Aug). Hypnotic visual illusion alters color processing in the brain. Am J Psychiatry, 157(8),1279-84. doi: 10.1176/appi.ajp.157.8.1279.

Peebles-Kleiger, M.J. (2000, May). The use of hypnosis in emergency medicine. Emerg Med Clin North Am, 18(2), 327-38, x. doi: 10.1016/s0733-8627(05)70128-0.

Rogovik, A.L. and Goldman, R.D. (2007, May). Hypnosis for treatment of pain in children. Can Fam Physician, 53(5), 823-5. Retrieved from: https://www.cfp.ca/content/53/5/823.long

Wain, H.J. and Amen, D.G. (1986, Jan). Emergency room use of hypnosis. Gen Hosp Psychiatry, 8(1), 19-22. doi: 10.1016/0163-8343(86)90059-9.

Wobst, A.H.K. (2007, May). Hypnosis and surgery: past, present, and future. Anesth Analg, 104(5), 1199-208. doi: 10.1213/01.ane.0000260616.49050.6d.

CHAPTER 18

ACTIVE AGING

M.D. Zeynep UNUS YILMAZ[1]

[1] Kaynarca Şehit Gökhan Ayder District State Hospital, Department of Family Medicine, Sakarya, Türkiye.
zeynepunus@gmail.com, Orcid ID: 0000-0003-0897-3555

INTRODUCTION

In recent years, the average life expectancy has increased due to the developments in the health sector, the increase in the income of individuals and the corresponding increase in welfare and social standards. (UN DESA, 2017). World Health Organization (WHO) described this increase as the most important achievement of humanity. The increase in life expectancy has brought with it issues that need to be emphasized in many areas, especially in social, cultural and economic areas. That's why aging is also considered to be our biggest struggle.

Worldwide, age groups, sixty and over are growing faster than others. WHO uses the United Nations age standard of sixty to describe "older" people. In 2002, 400 million people were living in the world, who were considered elderly. By 2025, this number is estimated to be around 840 million. (Figure 1) (WHO, 2002a)

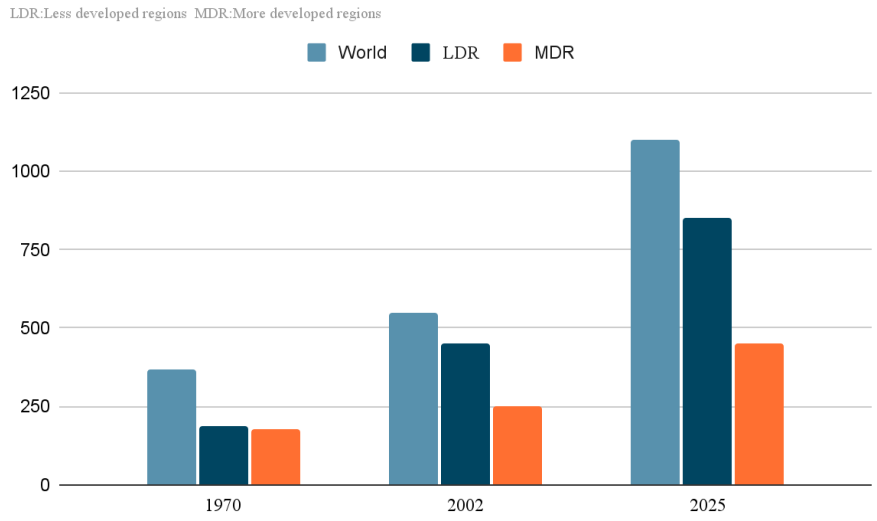


Figure 1. Number of older people living in less and more developed areas (WHO, 2002b)

Aging is a process that is expected to involve physical, psychological and social changes. It is also a global phenomenon meaning deep economic and social restructuring that requires coordinated action at the international, national, regional and local levels (Governance of Aging). (Walker, 2009) In response to the aging of the population, the global policy strategy is based on

'active aging'. Active aging can be defined as increasing the quality of life of elderly individuals, increasing their safety, protecting their health and increasing their participation in life. The word "active" in the definition is not used only in the physical sense. It is used to pursue social, economic, cultural, spiritual and civic affairs (WHO, 2002b).

In recent years, there has been a growing political interest in this issue, as well as increasing scientific knowledge. In this context, the focus was on developing and finding formulas that allow 'aging well' scientifically. At the same time, in the political sphere, there has been an increase in developing and finding formulas to give older people greater autonomy and sociability (Murtagh, 2017).

In the 1950s, a concept called "activity theory" was introduced in the literature. According to this theory, it has been argued that maintaining an active lifestyle in old age strengthens the individual's sense of personal satisfaction. Perspective life before this period; He divided it into three parts as “learning, working and resting” and described the old age period as the rest period. The concept of active aging was first used in the literature as a component of the concept of "successful aging" in the 1960s and was basically built on the theory of activity. In addition to the concept of active aging, the concepts of "successful aging", "healthy aging", "productive aging" are also used, and it is seen that these concepts are sometimes used interchangeably in the literature. However, activity theory has been criticized on the grounds that it is restricted to a single lifestyle(Bowling, 2008)

It is suggested that the activity theory excludes a group of elderly people who are not physically active enough due to health conditions. Similarly, the concept of "productive aging", which is criticized for excluding the elderly who are not working, and the concept of "successful aging", which is criticized as placing unrealistic expectations on individuals and stereotyping individuals, is also discussed (Ranzijn, 2010).

WHO emphasizes considering the frail elderly as well as the fit elderly and addressing active aging as a right rather than a necessity.

In addition, reducing the health expenditures of the elderly should not be adopted as the primary goal. It has been suggested to take action so that the elderly can live as productive and active members of the society. With this discourse, WHO emphasizes that older people should not only be physically

active, but also be included in the workforce and participate in social, economic, cultural, spiritual and civil life.

More emphasis is placed on active aging in the literature over the socioeconomic impact. However, the psychological and social aspects of active aging are of great importance. (United Nations Economic Commission for Europe (UNECE)., 2018)

Some authors consider that leisure activities within the context of this concept should also include learning activities, dealing with other family members, volunteer activities and finally political participation.(Baker et al., 2005; Boulton-Lewis et al., 2006; Higgins, 2005; Principi et al., 2014; Salari et al., 2006)

A health system that prioritizes active aging is recommended. This should ensure lifelong health promotion, disease prevention and equal access to primary and long-term care. Studies have tried to determine the determinants of active aging. These determinants are; culture, gender, economic factors, health and social services, social-environmental determinants, physical-environmental determinants, personal factors and behavioral factors (Figure 2) (WHO, 2002a).

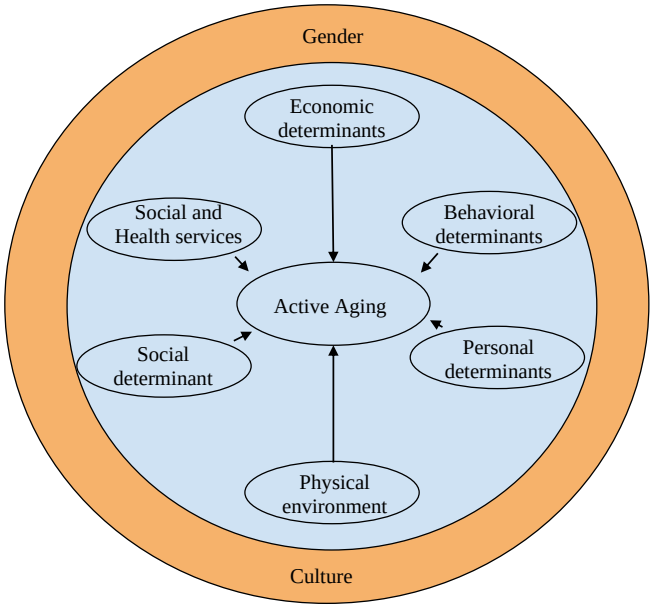


Figure 2. The determinants of Active Aging(WHO, 2002b)

Culture is seen as the most inclusive element in the concept of active aging, as it surrounds our entire life. How a society looks after the aging process and the elderly is shaped by its cultural values and traditions. When the disease symptoms seen in the society, especially in the elderly, are seen as a result of the aging process, they are less likely to provide prevention, early diagnosis and appropriate treatment services.

Living with extended families is culturally important, especially in Asian countries.

Policies around the world and in countries should aim to eliminate misinformation while respecting existing cultures and traditions. While respecting cultures, critical universal values that transcend culture, such as ethics and human rights, should be prioritized above all else.(WHO, 2002a)

Gender is a concept used to assess the relevance of various policy options to active aging and how these policies will affect gender-specific well-being. In many societies, women have lower social status, less access to food, education, meaningful work and health care. Traditionally, women take on the role of caregivers in their families, which increases their poverty in later life and can lead to poor health. Some women are forced to leave their paid jobs to meet the caregiver role expected of them. At the same time, women are more likely to be exposed to violence by men, resulting in disability injuries, occupational hazards, and even death (WHO, 2002b)

Social and health services should be integrated, communicative and cost-effective. While providing such services, age discrimination should not be made and service providers should treat people of all age groups with respect and dignity.

Health promotion is the process of enabling people to take control over and improve their own health. Disease prevention includes the prevention and management of conditions such as noncommunicable diseases and injuries that occur as individuals age. At the same time, they all contribute to reducing the risk of disability.(WHO, 2002a)

Despite all efforts, the risk of contracting diseases increases as people age. As we age, the need for treatment services becomes inevitable. In many countries, the vast majority of older people live in the community, most of whom receive health care from primary care providers. As the population ages, the need to delay and treat chronic diseases, reduce pain and improve quality of

life increases, and the demand for medicines will continue to increase. This increase in need requires a multidisciplinary effort to ensure access to medicines and better enable the appropriate and cost-effective use of medicines.

Long-term care is defined as “a system of recruiting non-professionals and/or professionals to provide care for a person who cannot fully care for himself/herself”. Long-term care includes the support of formal and informal systems.

An integral part of long-term care should be mental health services, especially attention should be paid to the diagnosis of depression.(WHO, 2002a)

It is an issue that the individual should actively participate in her/his own care and adopt a healthy lifestyle and care about. Aging individuals think that it is too late to change their behavior and change their lifestyle. Contrary to this belief, performing appropriate physical activity in old age, taking care of healthy eating, not using cigarettes and drugs, using alcohol wisely prevents diseases and functional regression. It is predicted to prolong the life of the person and increase the quality of life.(WHO, 2002a)

Aging is a genetically determined biological process. Therefore, biology and genetics greatly affect how one's old age will be (Gürsoy Çuhadar, 2020). While genes may be one of the causes of disease, for many diseases the cause is environmental and extrinsic rather than genetic and intrinsic.

One of the strongest predictors of active aging is cognitive capacity and intelligence.(Smits et al., 1999).In the normal aging process, these cognitive capacities naturally decline with age. However, these losses can be compensated by the person's intelligence capacity, knowledge and experience gains (WHO, 2002b)

Age-friendly physical environments are important for all individuals, but extra important for older individuals. Older people who have many physical disabilities and live in areas where they do not feel safe are less likely to leave the house. This can cause isolation, depression, decreased fitness and increased mobility problems in the elderly.

For older people, a safe environment means location, services and transport, positive social interaction, including proximity to family members. It is necessary to remove or eliminate household hazards that increase the risk of falling. Older people in developed countries often live alone. However, in other

countries, they live with their families in unsuitable and crowded houses.(WHO, 2002b)

Falls are the leading cause of injury, treatment cost, and death in older people. Poor lighting, slippery or uneven walking surfaces, and lack of supportive handrails are environmental hazards that increase the risk of falling. Most of the time, falls occur in the home environment and many of them are preventable.

Access to clean air, water and safe food is especially important for the elderly (WHO, 2002a).

The availability of social support, educational opportunities and lifelong learning opportunities in a society are the main factors that increase the health, participation and safety of the elderly. Insufficient social support in society increases the rates of psychological problems, diseases and even death. This was also associated with the same reduction in general health and well-being.

One of the important problems faced by the elderly is age discrimination and abuse. Elder abuse is a single or repeated occurrence of a damaging event from someone who has an expectation of trust from the older individual (McGough, 2011). According to the approach, elder abuse includes physical, sexual, psychological and financial abuse as well as neglect. A common form of violence faced by the elderly (especially older women) is elder abuse, often perpetrated by family members or caregivers.

The elderly, especially those who are frail and live alone, may feel particularly vulnerable to crimes such as theft and assault. It is emphasized that low education level and illiteracy are another factor that affects the higher unemployment rates, as well as the increased risk of disability and death among people as they age.

Education and lifelong learning early in life can help people develop the skills and confidence they need to adapt and stay independent as they get older. Intergenerational learning between older people and the younger generation bridges age differences, enhances the transmission of cultural values and enhances the value of all ages.(WHO, 2002a)

The economic environment is examined from three aspects: financial income, jobs and social protection. Many elderly people, especially women, living alone or in rural areas do not have sufficient income. Low income significantly affects access to nutritious food, adequate shelter and health care.

However, it is seen that old men and women who are part of families who do not have a pension or social security payment, have no assets, no savings, and do not have a regular and sufficient income, are also very vulnerable in this context (WHO, 2002a).

In terms of social protection, it is seen that the family institution is in a dominant position in getting the support that the elderly need. As the developing society structure and the tradition of generations living together begin to decline, the obligation of countries to develop mechanisms that provide social protection for elderly people who cannot make a living, who are lonely and vulnerable, emerges.

On the other hand, concentrating only on formal labor market work in the context of work relative to active aging undermines the valuable contributions older people make by working unpaid in the informal sector (for example, small-scale, self-employed activities and housework) and at home. However, it should be underlined that while voluntary work makes an important contribution to societies, it also benefits older people by increasing social relations and psychological well-being.

WHO bases its active aging policy recommendation on the tripartite pillars of health, participation and safety(WHO, 2002b)

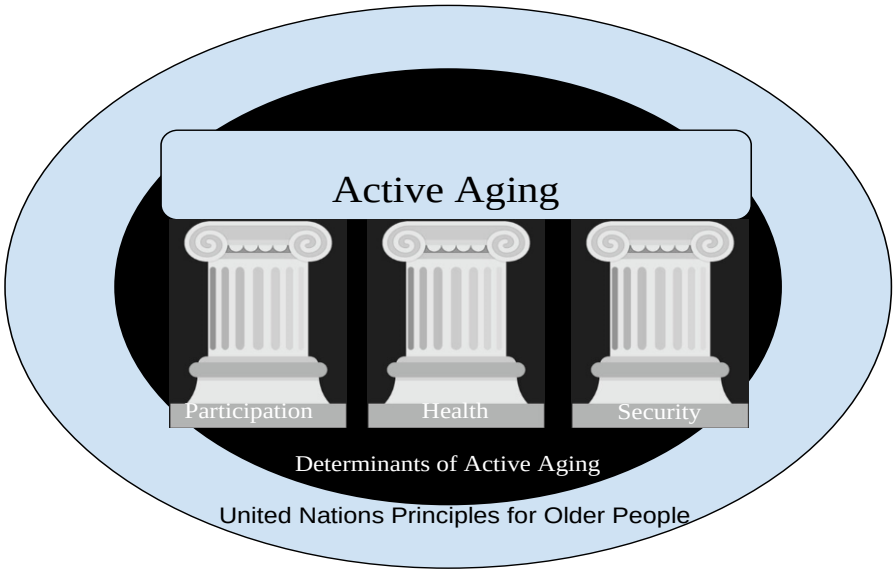


Figure 3. The three pillars of a policy framework for Active Aging (WHO, 2002b)

Approach to the **health pillar**; He claims that if environmental and behavioral factors are reduced and protective factors are increased for chronic diseases, the quality of life of people will increase both in terms of quantity and quality. Thus, less elderly will need expensive medical treatment and care services. It advocates that those in need of care should have access to all health and social services.

In the participation pillar of active aging, emphasis is placed on employment, education, health and social policy according to capacities, needs and preferences. It emphasizes that it should be done in a way that supports the participation of the elderly in socioeconomic, cultural and spiritual activities according to their fundamental rights. It is claimed that as people age, their participation in society will continue to be provided by paid and unpaid activities.(WHO, 2002b)

With regard to safety, it states that policies and programs must address the social, economic and physical security needs of people as they age.

WHO underlines that countries should produce policies that include active aging. When social policies including health, labor market, employment and education support active aging, there will potentially be less premature deaths, a decrease in chronic diseases encountered in older ages, the quality of life of more people will increase as they get older, and the elderly will be more involved in social, cultural, economic and political life. It is claimed that they will participate in the study and lastly, the costs of care and health services will decrease.

On the other hand, it should be underlined that active aging is not just a concept related to the inclusion of older individuals in the labor market, but also an approach to their active participation in society, both through voluntary work and the opportunity to live independently thanks to adapted housing and infrastructure.

The active aging approach provides a framework for the development of global, national and local strategies for population aging. It brings together health, participation and safety action, providing a consensus-building platform that addresses the concerns of multiple industries and entire regions. Policy proposals and recommendations are of little use unless they take action. That's why WHO says, 'Now is the time to act' (WHO, 2002a)

In the scientific literature, Active Aging is used as a definition to mean "productive", "healthy" or "successful" and limits this definition. However, it should be evaluated in terms of participation in social, economic, cultural, spiritual and civic issues and should be expanded in this context.

The adjective "active" is used to be the protagonist of one's own life and aging. From this point of view, it indicates that it is up to the person to develop his efficiency and capacity (Stenner et al., 2011). Man is an active representative of his own aging. Throughout life, a person interacts with an active world, evolving through a continuous and dynamic process(Casas, 2009). Despite its conceptual scope, we often take a one-dimensional approach to active aging and focus mainly on one aspect. For example, we approach from an economic point of view, by stating the extension of working life, and from a physical activity point of view as a way to improve health in old age. This reflects the concepts of 'Healthy Aging' and 'Productive Aging' mentioned in previous years (Boudiny & Mortelmans, 2011).

Various debates have emerged in research on active aging in the literature. There is disagreement over its definition. And also there is confusion about the determinants of the components(Boudiny, 2013; Tareque et al., 2013). There is controversy between active and passive activities (Boudiny & Mortelmans, 2011). In general, only active leisure activities are considered important in active aging (Colcombe & Kramer, 2003). However, many older people find that "normal" leisure activities based on home and family, often classified as passive, better represent their participation in life(Clarke & Warren, 2007).

Finally, as stated in the Fundación General Spanish National Research Council (FGCSIC) (s.2) report "the generation of knowledge related to the different facets of ageing of people and societies is essential to contribute to providing solid bases for decision-making processes, with the most integral perspective possible. Beyond prolonging longevity, the challenge is how to age healthily. At a global level, the biggest challenge is to support our elders so that healthy ageing is generalized and takes place in better conditions of personal independence, while facilitating them to continue contributing value to society" (CSICGeneralFoundation(FGCSIC), 2016)

REFERENCES

Baker, L. A., Cahalin, L. P., Gerst, K., & Burr, J. A. (2005). Productive activities and subjective well-being among older adults: The influence of number of activities and time commitment. *Social Indicators Research*, *73*(3). https://doi.org/10.1007/s11205-005-0805-6

Boudiny, K. (2013). "Active ageing": From empty rhetoric to effective policy tool. *Ageing and Society*, *33*(6). https://doi.org/10.1017/S0144686X1200030X

Boudiny, K., & Mortelmans, D. (2011). A Critical Perspective: Towards a Broader Understanding of 'Active Ageing.' *E-Journal of Applied Psychology*, *7*(1). https://doi.org/10.7790/ejap.v7i1.232

Boulton-Lewis, G. M., Buys, L., & Lovie-Kitchin, J. (2006). Learning and active aging. *Educational Gerontology*, *32*(4). https://doi.org/10.1080/03601270500494030

Bowling, A. (2008). Enhancing later life: How older people perceive active ageing? *Aging and Mental Health*, *12*(3). https://doi.org/10.1080/13607860802120979

Casas, F. (2009). Envejecer Activo. Contribuciones de la Psicología, R. Fernández Ballesteros, Pirámide 2009. *Psychosocial Intervention*, *18*(1). https://doi.org/10.5093/in2009v18n1a9

Clarke, A., & Warren, L. (2007). Hopes, fears and expectations about the future: What do older people's stories tell us about active ageing? *Ageing and Society*, *27*(4). https://doi.org/10.1017/S0144686X06005824

Colcombe, S., & Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults: A meta-analytic study. *Psychological Science*, *14*(2). https://doi.org/10.1111/1467-9280.t01-1-01430

CSICGeneralFoundation(FGCSIC). (2016). *Aging Research Report*. *(Acessed on 21.12.2022)*

Gürsoy Çuhadar, S. (2020). Yaşlanan Nüfusa Çözüm Önerisi Olarak Aktif Yaşlanma Yaklaşımı: Eleştiriler ve Olası Endeks için Türkiye Önerileri. *Sosyal Siyaset Konferansları Dergisi/Journal of Social Policy Conferences*. https://doi.org/10.26650/jspc.2020.79.0004

Higgins, J. (2005). Exploring the politics and policy surrounding senior center gambling activities. *Journal of Aging Studies*, *19*(1). https://doi.org/10.1016/j.jaging.2004.01.009

McGough, G. (2011). Action on Elder Abuse. *Nursing Standard*, *26*(1). https://doi.org/10.7748/ns2011.09.26.1.28.p6373

Murtagh, B. (2017). Ageing and the social economy. *Social Enterprise Journal*, *13*(3). https://doi.org/10.1108/sej-02-2017-0009

Principi, A., Jensen, P. H., & Lamura, G. (2014). Active ageing: Voluntary work by older people in Europe. In *Active Ageing: Voluntary Work by Older People in Europe*. https://doi.org/10.1007/s40718-015-0023-5

Ranzijn, R. (2010). Active Ageing —Another Way to Oppress Marginalized and Disadvantaged Elders? *Journal of Health Psychology*, *15*(5). https://doi.org/10.1177/1359105310368181

Salari, S., Brown, B. B., & Eaton, J. (2006). Conflicts, friendship cliques and territorial displays in senior center environments. *Journal of Aging Studies*, *20*(3). https://doi.org/10.1016/j.jaging.2005.09.004

Smits, C. H. M., Deeg, D. J. H., Kriegsman, D. M. W., & Schmand, B. (1999). Cognitive functioning and health as determinants of mortality in an older population. *American Journal of Epidemiology*, *150*(9). https://doi.org/10.1093/oxfordjournals.aje.a010107

Stenner, P., McFarquhar, T., & Bowling, A. (2011). Older people and "active ageing": Subjective aspects of ageing actively. *Journal of Health Psychology*, *16*(3). https://doi.org/10.1177/1359105310384298

Tareque, M. I., Hoque, N., Islam, T. M., Kawahara, K., & Sugawa, M. (2013). Relationships between the active aging index and disability-free life expectancy: A case study in the rajshahi district of Bangladesh. *Canadian Journal on Aging*, *32*(4). https://doi.org/10.1017/S0714980813000494

UN DESA. (2017). World Population Prospects: The 2017 Revision, Key Findings and Advance Tables. *United Nations*. *(Acessed on 21.12.2022)*

United Nations Economic Commission for Europe (UNECE). (2018). *Introducing the Active Ageing Index.* Https://Ec.Europa.Eu/Eip/Ageing/Library/Policy-Brief-Introducing-Active-Ageing-Index_en . *(Acessed on 21.12.2022)*

Walker, A. (2009). Commentary: The emergence and application of active aging in Europe. *Journal of Aging and Social Policy*, *21*(1). https://doi.org/10.1080/08959420802529986

WHO. (n.d.). *World Health Organization. (2002). Active ageing : a policy framework. World Health Organization.(Acessed on 21.12.2022)*

CHAPTER 19

DECONTAMINATION METHODS IN THE INTOXICATED PATIENTS

Res. Asst. Fatmanur ÇAVDAROĞLU[1]
Asst. Prof. Dr. Ali AYGUN[2]

[1] Ordu University, Faculty of Medicine, Department of Emergengy Medicine, Ordu, Turkey. fatmanurcavdaroglu96@gmail.com, ORCID ID: 0000-0003-0906-0002
[2] Ordu University Faculty of Medicine, Department of Emergengy Medicine, Ordu, Turkey. dr_aliaygun@hotmail.com, ORCID ID: 0000-0002-5190-1445

INTRODUCTION

Decontamination is defined as the removal of toxic substances from the body and the prevention of their absorption into the systemic circulation. Decontamination methods are divided into as skin or external, eye decontamination, gastrointestinal decontamination (1).

Tablo 1. Decontaminations methods

External/Skin Decontamination
Ocular decontamination
Gastrointestinal decontamination

1.External/Skin Decontamination

It is a method used in cases where the toxic substance is exposed through the skin or enters the systemic circulation through the skin. All clothes of patients who are exposed to external toxins should be removed after the health personnel take personal protective measures and the whole body should be washed with plenty of water (1). Contaminated clothing must be placed in at least a double layer of plastic bags. Soap is especially used to clean substances that are difficult to clean with high viscosity water from the skin (1). However, there are substances that water should not be used for skin decontamination.These substances are alkali metals reacting with water, reactive metallic forms of lithium, cesium and rubidium, and powders of pure magnesium, sulfur, strontium, titanium, uranium, yttrium, zinc and zirconium.These agents will ignite or explode on contact with water. These metals should be mechanically removed from exposure with forceps, gauze or towel in a dry manner (1,2).

Plastic, paint, rubber, phenol are difficult to remove after exposure to water. For the decontamination of phenol, it is recommended to alternately wash with water and polyethylene glycol (PEG 400) or 70% isopropanol for a total of 15 minutes, 1 minute each. Calcium oxide (quicklime) thickens after exposure to water and forms Ca(OH)2, emits heat and can cause cutaneous ulcerations, so mechanical removal is recommended, as is the case with other water-reactive substances (1,2).

2.Ocular Decontamination

The first approach to all ocular caustic exposures is to provide eye irrigation by flushing with plenty of water. Apart from water, saline, ringer lactate or balanced salt solutions can also be used for eye washing. In toxic eye injuries, local anesthetics (eg, 0.5% tetracaine) can be dripped to reduce the pain that may occur during the eye irrigation procedure, and the eyelids can be lifted with the help of lid retractors for more effective washing. Eyewash should include not only the outer and inner palpebral surfaces, but also the cornea and bulbar conjunctiva and its recesses. Visual acuity test, eye examination and slit-lamp examination should be performed after irrigation.

The first approach in all eye decontamination procedures should be irrigation with copious amounts of saline for at least half an hour. Anesthetic eye drops may be used during this irrigation. In the case of ocular corrosive substance irrigation, an acidic substance should not be neutralized with an acidic substance or a basic substance with an acidic substance. We have four purposes in the decontamination process of the eye: irrigation of the toxic substance with copious washing; removal of the substance causing toxicity; removal of any ocular foreign body; in some special cases, ensuring that the anterior chamber pH comes to normal. In addition to the outer and inner palpebral surfaces, the cornea and bulbar conjunctiva and its recesses should also be included in the washing process of the eye. After eye decontamination, a detailed eye examination should be done. In case of contact of corrosive substances with the skin, an acidic substance should not be tried to be neutralized with an acidic substance. Because the heat reaction that may occur can cause more damage to the skin (2).

3. Gastrointestinal Decontamination

Gastrointestinal decontamination is the most common method of decontamination applied to patients in hospital admissions due to intoxication. There are questions that we need to review when starting the gastrointestinal decontamination method in cases of oral poisoning. Did they cause serious toxicity in the event of poisoning? Does the gastrointestinal decontamination method benefit the case of poisoning? Is the probability of the action to be harmful more likely to be harmful than beneficial?

Although scientific studies show that GI decontamination prevents drug absorption, it does not significantly benefit patients' mortality and hospital stay. It is known that the effectiveness of GI decontamination decreases as the

duration of ingestion of the toxic substance causing poisoning and the duration of hospitalization are prolonged (2).

Tablo 2.Gastrointestinal Decontaminations

Emezis
Gastric lavage
Activated CharcoaL
Whole-Bowel Irrigation

3.1.Gastrointestinal decontamination/Emesis

Ipeca contains alkaloids from the plants cephalis acuminata and cephalis ipecacuanha. In addition to its gastric irritation effect, İpeka also causes vomiting by stimulating the chemoreceptors in the brain thanks to the emetine and cephalin it contains. Ipeca syrup is taken orally and has a GI decontamination effect with vomiting effect. The recommended dose for adult patients is a dose of 30 mL with 16 oz of fluid (repeated every 20 minutes if vomiting is not present). For children aged 1-12, 15 mL with 6-8 oz of liquid, and 10 mL with 4 oz of liquid for 6-12 months old babies is the effective dose for vomiting. Although the vomiting process occurs with full success, it does not completely prevent the elimination of the toxic substance. If vomiting occurs within the first 30 minutes after Ipeca syrup application, a higher rate of removal of the toxic substance can be achieved. The most serious side effects of ipecac are aspiration pneumonia, bronchospasm, Mallory-Weiss tears in the esophagus, bradycardia, and mediastinal barotrauma, which occur after repeated episodes of vomiting lasting longer than 60 minutes. However, studies have shown that emesis in the emergency room after poisoning does not help, so emesis is not indicated in hospital admissions with a case of poisoning (2).

The contraindications;

- Having activated charcoal or another oral treatment
- In case the airway is unprotected or will disappear in a short time
- Caustic substance intake
- Swallowing a medicine pack or a sharp foreign object
- Ingestion of a xenobiotic with high aspiration potential such as hydrocarbon.
- Infants under <6 months, elderly or debilitated patients.

- If the patient has an additional disease in which morbidity may increase after vomiting (2)

3.2. Gastrointestinal decontamination/Gastric lavage

Gastric emptying is a method of GI decontamination that prevents or minimizes the potential toxic effect by removing the toxic substance before it is absorbed in the gastrointestinal tract. In general, it should be applied if there is no contraindication in the intake of life-threatening toxic substances that come within an hour.

Orgastric lavage is usually performed in the left lateral decubitus position using 36-40 french tubes in adult patients and 22-28 french tubes in pediatric patients. The most preferred liquid for lavage is made with room temperature water or physiological saline. The lavage process is continued until the water flowing out is clear. If there is an indication, activated charcoal should also be applied before the lavage tube is removed (2).

The contraindications

- A patient who is unconscious, without airway protection, or in need of intubation with an unsecured airway. (Gastric lavage should be applied if there is an indication after intubation)
- In corrosive material purchases
- Swallowing a foreign object (eg a medicine pack, sharp object)
- Ingestion of a xenobiotic with high aspiration potential (eg, a hydrocarbon) in an airway compromised patient
- Patient with signs or risk of gastrointestinal perforation
- Ingestion of a substance known to be too large to fit in the lavage lumen (4-9)

In patients without airway reflex, lavage is performed after intubating with a cuffed endotracheal tube and ensuring airway safety. Gastric lavage is not routinely recommended for all poisonings. It can be considered in patients who apply to the hospital within 1 hour after ingestion of toxic substances. However, in cases such as taking substances that delay gastric emptying with its anticholinergic effect and taking too many tablets, gastric lavage can be performed for up to 2 hours. Complications of gastric lavage include aspiration, laryngospasm, mechanical injury, and electrolyte disturbances (4-9).

3.3. Gastrointestinal decontamination/Activated charcoal

Activated Charcoal (AC) is a carbon-containing substance that is formed by processing coconut shell, coal or some other materials under high temperature without contact with air. Its surface area (3000 m2/gr) is quite large and has the ability to hold and bind some materials. Therefore, the basic mechanism of activated charcoal is to prevent many toxins from being absorbed from the gastrointestinal tract and passing into the systemic circulation. The adsorption rate varies according to the outer surface area and adsorption capacity. Capacity can be changed by changing the size of the pores. Activated charcoal products have pore sizes ranging from 10 to 1000 angstroms, with most of the inner surface area being 10 to 20 inches of pores. Many toxicants have a medium molecular weight (100-800 daltons) and can adsorb well in pores in the 10 to 20 A range (2).

Activated charcoal should be administered within the first 1 hour for absorbable or non-absorbable drugs in patients with airway safety. If the ingested substance has anticholinergic activity, has an extended release formulation and is in large amounts, this period can be increased to over 1 hour. AC application dose is 0.5-1 g/kg in children and 25-100 g in adults, or a single dose of AC from 1gr/kg can be applied. AC application can also be done by mixing it in fruit juice (9).

The contraindications;

- Intake of pure petroleum, hydrocarbons, and pesticides combined with hydrocarbons that are not adsorbed by activated charcoal.
- If esophageal or gastric perforation is suspected
- Ingestion of corrosive substances requiring urgent endoscopy
- Isolation uptake of heavy metals that are not adsorbed with activated charcoal (2)

3.4. Gastrointestinal decontamination/ Whole bowel irrigation

Xenobiotics that provide intestinal irrigation are called laxatives, cathartics, laxatives, stimulant agents and evacuators. Although all of these substances have intestinal irrigation effects, they all have different side effects. Laxatives provide a soft shaped or semi-liquid stool within 6 hours to 3 days, depending on the type and dose of the substance. Cathartics produce rapid, watery bulky stools within 1-3 hours." Irrigating agents such as promotility agents (acetylcholine, serotonin, motilin) are often used to cleanse the bowel before a procedure, with onset of action occurring in as little as 30

to 60 minutes, but more completely Application typically before 4 hours is required for an effect.

In cases of poisoning, the most effective procedure for patients to empty the intestinal passage is by administering polyethylene glycol 3350 (PEG), called a whole bowel lavage (WBI), typically added to a balanced electrolyte lavage solution (PEG-ELS) (2).

All bowel irrigation is done with polyethylene glycol (Golytely). Polyethylene glycol is an osmotically balanced electrolyte solution that does not allow fluid and electrolyte transport in the intestinal mucosa. With enteral administration in high volume, it reduces intestinal absorption of toxins and prevents systemic absorption by accelerating passage. This decontamination method is indicated for high-dose drug intake with an extended release, enteric-coated formulation, heavy metal intakes such as iron, lead, zinc, and lithium that activated charcoal cannot bind, or those who swallow illegal drug packages. The patient should sit or the head of the bed should be elevated; cathartic should be administered via a 12-French nasogastric tube. Whole bowel irrigation may be continued at an infusion rate of 1.5-2 L/hour in adult patients (500-1000 mL/hour in pediatric patients) for 4-6 hours (or 3 L) until rectal stool is clear. In case of vomiting, metoclopramide can be administered. In addition, the infusion rate can be reduced by 50% for up to 1 hour and then returned to the original rate. In cases where the orally ingested toxicant is with a toxin that cannot be well adsorbed by activated charcoal administered within 2 hours, it should be considered as a first-line GI decontamination method. Contraindications include adynamic ileus, bleeding, bowel obstruction, bowel perforation, unprotected airway, hemodynamic instability or uncontrolled vomiting. Activated charcoal should not be administered with whole bowel irrigation (2).

The contraindications;

- Patients without airway reflex or airway safety
- Patients with signs of ileus, obstruction, significant GI bleeding, or hemodynamic instability that may compromise gastrointestinal tract (GI) motility
- Persistent vomiting attacks
- Signs of leakage from cocaine packets (indication of surgical removal) (2-6)

KAYNAKÇA

1. Olson K, ed. *Poisoning & Drug Overdose.* 7th ed. Mc Graw-Hill Education; 2017.
2. Nelson L, ed. *Goldfrank's Toxicologic Emergencies*. 11th ed. Mc Graw-Hill Education; 2019.
3. Eddleston M, Haggalla S, Reginald K, et al. The hazards of gastric lavage for intentional self-poisoning in a resource poor location. *Clinical Toxicology*. Published online January 2007:136-143. doi:10.1080/15563650601006009
4. Pond S, Lewis-Driver D, Williams G, Green A, Stevenson N. Gastric emptying in acute overdose: a prospective randomised controlled trial. *Med J Aust*. 1995;163(7):345-349. doi:10.5694/j.1326-5377.1995.tb124625.x
5. Eddleston M, Juszczak E, Buckley N. Does gastric lavage really push poisons beyond the pylorus? A systematic review of the evidence. *Ann Emerg Med*. 2003;42(3):359-364. doi:10.1016/s0196-0644(03)00440-2
6. Albertson TE, Owen KP, Sutter ME, Chan AL. Gastrointestinal decontamination in the acutely poisoned patient. *Int J Emerg Med*. Published online October 12, 2011. doi:10.1186/1865-1380-4-65
7. Benson BE, Hoppu K, Troutman WG, et al. Position paper update: gastric lavage for gastrointestinal decontamination. *Clinical Toxicology*. Published online February 18, 2013:140-146. doi:10.3109/15563650.2013.770154
8. Kekeç Z, ed. *Acil Tıp Pratiğinde Klinik Toksikoloji*. 1st ed. Ema Tıp Kitapevi; 2020.
9. Satar S, Güneysel Ö, Yürümez Y, Türedi S, eds. *Klinik Toksikoloji Tanı ve Tedavi*. 1st ed. Nobel Tıp Kitabevi; 2020.

CHAPTER 20

GERIATRIC DEPRESSION

Dr. Zuhal KOÇ APAYDIN[1]

[1]Karabük University, Faculty of Medicine, Department of Mental Health and Diseases. Karabük, Türkiye. zuhalapaydin@karabuk.edu.tr, Orcid ID: 0000-0003-3893-5314

GERIATRIC DEPRESSION

Major depressive disorder is an important mental disorder that leads to disability and impaired functioning all over the world (1). Studies have suggested that depressive symptoms are associated with structural and neurochemical deficiencies in corticolimbic brain regions (2-4) It is a disorder characterized by depressed mood that lasts throughout the day, anhedonia, changes in weight and appetite, sleep disorders, cognitive disorders such as loss of energy, forgetfulness and loss of concentration, psychomotor agitation or retardation, thoughts of death and self-harm, sense of guilt, worthlessness and pessimistic thoughts.

Nowadays, the increase in the elderly population, secondary to the improvement of technology and living conditions, also increases the interest in diseases seen in the elderly population and causes the search for diagnosis and treatment. While the 12-month incidence of major depressive disorder is 7%, this rate is 3 times more common in the elderly population (5). Again, considering the symptoms that meet the diagnostic criteria for depression in the elderly, it is estimated that the prevalence is between 1-5%, especially in the group over the age of 60 and 65 (6) and it is estimated that depressive symptoms that do not meet the diagnostic criteria are 2-3 times more (7). Although depression is one of the most common mental disorders in the elderly, the fact that these symptoms cannot be recognized very well with age, the fact that these symptoms are seen as the usual symptoms of old age pushes the importance of the issue to the background, making it difficult for patients to seek treatment and its prospects. Getting to know geriatric depression more closely and researching treatment methods will make a positive contribution to the quality of life of the elderly population in the future.

Epidemiology of Depression in the Geriatric Population

As mentioned earlier, the prevalence of depressive disorder is 1-5%, especially in the group over the age of 60-65(6). In elderly people who have a medical disease and are therefore receiving treatment, the incidence of depression has been reported to vary between 7% and 42% (8).

Female gender, living alone, insufficient social support and low socio-economic level are also closely related to old age depression (9).

Etiology of Depression in the Geriatric Population

Although many factors play a role in old age depression, it is known that genetic factors play a lesser role. Chronic, vascular, immunological diseases that increase with age, drugs used in the treatment of these diseases, physiological changes that develop due to old age, losses, incapacitation, living alone, low socio-economic level, female gender, disorders in cognitive

functions that increase with old age, chronic pain and sleep disorders are considered among the causes of depression in the elderly population (10,11)

In addition to the fact that chronic diseases cause depression, senile depression is more common in cases that also increase dependence on other people, such as Parkinson's, stroke, cancers, neurodegenerative diseases (12). Furthermore, the decrease in serotonin, noradrenaline, dopamine and GABA concentrations that occur in the central nervous system with old age creates a tendency to depression (13).

Lack of social support, especially in the elderly population accompanied by cognitive impairment, negative life events experienced in the last year increase the likelihood of developing depression (14) Again, it has been found that the development of depression is more common in inpatients and in the elderly population staying in nursing homes (15).

Clinical Appearance of Depression in the Geriatric Population

In major depressive disorder, patients have sad facial expressions, speak in a quiet low tone of voice, often do not even want to talk, have a deep sadness and suffering. There are inactive, forgetful, inability to collect attention situations. Their speed of thought has slowed down. It can be accompanied by thoughts of helplessness, pessimism and hopelessness. As they lose their self-esteem, the accompanying suicidal thoughts may follow the situation. Although psychomotor retardation is mostly seen, there are also psychomotor agitation states accompanied by restlessness in some patients. In most patients, the desire to eat has decreased, weight loss can be observed, while in cases with atypical features, increased appetite and weight gain can also be observed. In addition, problems falling asleep, maintaining sleep, or escaping from negative thoughts and signs of weakness are observed. On the other hand, excessive sleeping behaviors can also be seen (5,16).

There are some differences in geriatric depression compared to depression in adulthood. Studies investigating the differences of geriatric depression compared to other adult depression have shown that while in the elderly, hypochondriasis, general and gastrointestinal somatic complaints, agitation is more common, it has been found that the complaints of guilt and loss of sexual desire (17). Again, in elderly patients, , there are sleep disorders such as waking up early especially during the day, mood swings are hidden, and instead there are symptoms that can range from somatic complaints to somatic delusions, the picture of the disease is more common than in adults (12).

Another type of depression that is especially common in the elderly over the age of 60 is depression with psychotic characteristics. In this type of depression, the frequency of which varies between 30-45%. There is a

treatment-resistant picture, especially accompanied by nihilistic, somatic, sense of guilt and paranoid delusions, but hallucinations are relatively less common (18).

Also in the clinical presentation called pseudodementia, which is one of the most common causes of cognitive impairment in the elderly, there is a picture that causes a deterioration in planning, executive functions, and a negative impact on memory. The picture is often accompanied by symptoms of retardation, delusions compatible with depressive mood, hopelessness, helplessness, and anxiety. Although this clinical appearance responds positively to treatment, it can also prepare the ground for the development of dementia in untreated cases (12,19).

Another subtype has been identified, which is called vascular depression due to the frequent accompany with vascular brain pathologies, especially in elderly depression, and in this subtype, in particular, there is a deterioration in executive functions, psychomotor retardation, neurological disorders, accompanying vascular pathologies, resistance to treatment and poor prognosis (18,20).

In addition, suicide is an important problem in depression seen in elderly age. It is known that about 20% of all suicides are at an advanced age. The presence of cognitive losses, chronic diseases, structural anomalies in brain imaging cause depression to be more severe and persistent, and in this case, advanced age is an important factor for suicidal behaviors (16).

Diagnosis of Geriatric Depression

Making a diagnosis of geriatric depression involves some difficulties compared to younger patients. For instance, cases such as the patient, patient relatives and physicians accepting the symptoms of depression as a natural process of old age, and the fact that old age depression shows some differences compared to adulthood depression, the conditions related to the physical diseases that arise make it difficult to clarify the situation can be counted.

In elderly depression, as in adult depression, it is one of our priority preferences to make a diagnosis according to the DSM-5 criteria.

DSM-5 Major Depressive Disorder Diagnostic Criteria

A. During the same two-week period, at least five (or more) of the following symptoms are present and there has been a change in the previous level of functionality. At least one of these symptoms is (1) depressed mood or (2) loss of interest or pleasure.

1- The presence of a depressive mood that occurs almost every day, most of the day, subjectively reported by the person or observed by others

2- Marked decrease in interest in all or almost all activities almost every day, most of the day, or inability to enjoy activities
3- Losing a lot of weight or gaining weight when not dieting, or almost every day, a decrease or increase in appetite
4- Insomnia or excessive sleep almost every day
5- Almost every day, psychomotor agitation or retardation
6- Almost every day, fatigue or decreased energy.
7- Almost every day, feelings of worthlessness or excessive or inappropriate guilt
8- Almost every day, difficulty thinking or concentrating, or indecision
9- Repetitive thoughts of death, repetitive thoughts of suicide, or making a specific plan to kill yourself

B. These symptoms cause clinically significant distress or impairment in social, work-related areas or other important areas of functioning.
C. This period cannot be attributed to the physiological effects of a substance or other medical condition.
D. Major depressive period cannot be explained better in schizoaffective disorder, schizophrenia, an anxiety disorder, delusional disorder, or schizophrenia spectrum disorders within the scope of designated or undesignated other disorders with psychotic disorders
E. There has never been a manic or hypomanic episode (5).

Apart from the DSM-5 diagnostic criteria, some scales that allow measuring the diagnosis and severity of depression are also mentioned below.

Hamilton Depression Scale: It is a scale applied to the patient by the interviewer consisting of 17 items containing symptoms of major depressive disorder such as feelings of guilt, suicidal thoughts, anxiety, depressed mood (22).

Beck Depression Inventory: It is a self-report scale consisting of 21 questions evaluating depressive symptoms and attitude. It provides information about the severity of depression (23).

Geriatric Depression Scale: It is a questionnaire form used to measure the presence and severity of depression in the elderly population consisting of 30 item questions (24).

Treatment of Geriatric Depression

While the patient's treatment is provided for depression in the advanced age period, accompanying disease, the physical condition of the person, the medications he uses, the risk of suicide should definitely be taken into account. If the patient's physical condition is poor, if he does not have social support, treatment may be required by hospitalization in cases of accompanying delusions, cognitive impairment, treatment incompatibility.

Before starting treatment in the elderly population, a detailed physical examination and evaluation of the cardiovascular system, kidney, liver, thyroid functions should be conducted. It should be kept in mind that many physical illnesses can be accompanied by depression. Serotonin reuptake inhibitors should come to mind first in psychopharmacological treatment (25). However, the pharmacokinetic effects in adults and the effects in the elderly are different from each other (26). In addition, the side effects of antidepressants such as nausea, constipation, dizziness, headache and sleep disturbance affects antidepressant adherence among geriatric populations by increasing the rate of antidepressant replacement rate and withdrawal (27). Therefore, the study of the overall effectiveness of antidepressant drugs in elderly people is a must.

In studies comparing SSRI drugs in the elderly patient population, it was found that sertraline treatment is less risky (28). In this sense, SSRI can be used as one of the first choices. Antipsychotics can be added to the treatment in depression with psychotic symptoms, as well as electroconvulsive therapy can be tried in the treatment of cases such as the presence of psychotic symptoms, psychomotor retardation, refusal to eat and drink.

In addition to pharmacotherapy, cognitive-behavioral therapy, interpersonal therapies, whose effectiveness has been proven, especially in major depressive disorder, can be added to the treatment alone or in combination (21).

REFERENCES

1. Menard, C., Hodes, G.E., Russo, S.J. (2016) Pathogenesis of depression: Insights from human and rodent studies. *Neuroscience*, *321*, 138–162.
2. Russo, S.J., Nestler, E.J. (2013) The brain reward circuitry in mood disorders. Nat. Rev. Neurosci., 14, 609–625.
3. Krishnan, V., Nestler, E.J. (2008) The molecular neurobiology of depression. Nature, 455, 894–902.
4. Schmidt, H.D., Shelton, R.C., Duman, R.S. (2011) Functional biomarkers of depression: Diagnosis, treatment, and pathophysiology. Neuropsychopharmacology, 36, 2375–2394.
5. American Psychiatric Association. (2015). *Depressive disorders: DSM-5® selections*. American Psychiatric Pub.
6. Thomas A. (2013) Depression in older people. Oxford Textbook of Old-age psychiatry. Oxford: Oxford University Press, 544–69.
7. Meeks TW, Vahia IV, Lavretsky H et al. (2011) A tune in "a minor" can "b major": a review of epidemiology, illness course, and public health implications of subthreshold depression in older adults. J Affect Disord; 129: 126–42.
8. Bagley H, Cordingley L, Burns A et al. (2000) Recognition of depression by staff in nursing and residential homes. J Clin Nursing, 9:445-450.
9. Schoeverrs RA, Geerlings MI, Beekman ATF et al. (2000) Association of depression and gender with mortality in old age. Br J Psychiatry, 177:336-342.
10. Cole, M. G., Dendukuri, N. (2003). Risk factors for depression among elderly community subjects: a systematic review and metaanalysis. *Am J Psychiatry*, 160: 1147-1156.
11. Hacıhasanoğlu R., Yıldırım A., (2009). Depression and affecting factors in the elderly living in Erzincan Nursing Home. *Turkish Journal of Geriatrics*;12(1):25– 30.
12. Tamam, L. ve Öner, S. (2001). Old age depressions. Journal of Dementia; 1 (2), 50 60.
13. Janzing, J., Teunisse, R., Bouwens, P. (2000). The Course of Depression in Elderly Subjects With and Without Dementia. *J Affect Disord*.; 57(1-3):49-54.
14. Beekman, A. T., Copeland, J. R., Prince, M. J. (1999). Review of community prevalence of depression in later life. *Br J Psychiatry*, 174:307-311.
15. Morse, J. Q., Robins, C. J. (2005). Personality-Life event congruence effects in late life depression. *Journal of Affective Disorders*.; 84,25-31

16. Öztürk, M. O., & Uluşahin, A. (2015). Mental health and disorders. Mood Disorders. Nobel Medical Bookstores; 264-268.

17. Hegeman JM, Kok RM, van der Mast RC, et al. (2012). Phenomenology of depression in older compared with younger adults: Meta-analysis. Br J Psychiatry.; 200(4):275-281.

18. Alexopoulos GS. (2000) Mood disorders. Comprehensive Textbook of Psychiatry, BJ Saddock, VA Saddock (Ed), 7th edition, Philadelphia, Lippincott Williams and Wilkins, s.3060-3067.

19. Öztürk, Z. A. (2022). *Pratic Geriatri*. Prof. Dr. Zeynel Abidin öztürk. Galenos yayınevi tic. Ltd. şirk.: 18-20.

20. Tiemeier, H. (2003). Biological Risk Factors for Late Life Depression. Eur J Epidemiol.; 18:745-50.

21. Işık E., Işık U., Taner Işık Y. (2013). Depressive and Bipolar Disorders in Children, Adolescents, Adults and the Elderly. Rotatip Bookstore Trade. Ltd. Sti. 585-586.

22. Hamilton M.A. (1960) A Rating Scale for Depression. J Neurol Neurosurg Psychiatry, 23: s. 56-62.

23. Beck A.T. et al. (1961) An inventory for measuring depression. Arch Gen Psychiatry, 4: s. 561-71.

24. Yessevage JA, Brink TL, Rose TL et al. (1983) Developement and validation of a geriatric screening scale: a preliminary report. J Psychiatric Research;17(1):37-49

25. Kok, R.M., Reynolds, C.F., 2017. Management of depression in older adults: a review. JAMA 317, 2114–2122

26. Harvey A.T., Preskorn, S.H., 2001. Fluoxetine pharmacokinetics and effect on CYP2C19 in young and elderly volunteers. J. Clin. Psychopharmacol. 21, 161–166

27. Mark, T.L., Joish, V.N., Hay, J.W., Sheehan, D.V., Johnston, S.S., Cao, Z., 2011. Antidepressant use in geriatric populations: the burden of side effects and interactions and their impact on adherence and costs. Am. J. Geriatr. Psychiatry 19, 211–221.

28. Hsu, C. W., Tseng, W. T., Wang, L. J., Yang, Y. H., Kao, H. Y., & Lin, P. Y. (2022). Comparative effectiveness of antidepressants on geriatric depression: Real-world evidence from a population-based study. *Journal of Affective Disorders*, *296*, 609-615.

CHAPTER 21

FACTORS AFFECTING HEAD TRAUMA AND PROGNOSIS IN THE GERIATRIC PATIENT POPULATION

Phd. MD. Aydın Sinan APAYDIN[1]

[1]Karabük University, Faculty of Medicine, Department of Neurosurgery, Karabük, Türkiye. dr.sinanapaydin@yahoo.com, Orcid ID: 0000-0002-2916-9550

Old age is accepted as an irreversible process of human life. While the United Nations (UN) defines old age as 60 years and older, the World Health Organization (WHO) defines 65 years and older as old by setting a chronological limit (1). In addition, WHO predicts that the number of people aged 60 and over will double by 2050 (2). In Japan, it is expected that 32% of the population will be elderly by 2050 (3). Moreover, according to other statistical information, in 2015, 8.5% of the entire world's population consists of the elderly. According to the elderly population density ratio, Turkey ranks 66th with a rate of 8.2% among 167 countries in the ranking, and it is known that in 2015, the number of elderly individuals who are 100 years and over was 5,293. It is estimated that the proportion of the elderly population will reach 10.2% in Turkey by 2030 and 20% by 2050 (4).

For this reason, as in developed countries, health services for the ever-increasing elderly population in our country are increasing. The increase in the elderly population has made it necessary to better perceive the problems of this particular population.

The number of geriatric patients aged 65 and over admitted to emergency departments is increasing day by day. In different studies, emergency department admission rates of geriatric patients have been reported as 9-19% (5 - 7). According to the data of the National Center for Health Statistics (NCHS), 55.8% of the elderly admitted to the emergency department are 75 years of age or older (8). It is extremely crucial to make plans in order to provide appropriate services to this geriatric patient population and to use resources more positively in the future.

One of the most important health problems of the geriatric patient population is Trauma. Among the traumas, head injuries are among the conditions that emergency department physicians frequently encounter, which may have high mortality and morbidity (9). Head injuries are high in terms of mortality and morbidity in the geriatric patient population with isolated head trauma or multitrauma. It is certain that these problems are increasing and will increase with the effects of urbanization, the increase in motor vehicles, the extension of life expectancy and the rise in the prevalence of systemic diseases today (10).

As in all age groups, it is known that head trauma is the most important cause of mortality in the elderly population, after cardiac causes, cancer and

stroke. In clinical studies conducted in our country, the geriatric patient population accounts for 9.0%-23% of emergency department admissions (11). In a study conducted abroad, it was determined that the applications of patients aged 65 years and older constitute 15% of all emergency department applications (12). It is a serious problem in terms of economic as well as mortality and morbidity in isolated or multitraumas that we meet in the geriatric patient population. Traumas, which constitute a significant part of emergency department applications, cause increasing socioeconomic problems as a result of the long duration of examination and treatment along with the aging of the population and high morbidity rates.

HEAD TRAUMAS AND CLASSIFICATIONS

Head traumas are the result of the application of an external force to the cranium and its contents and cause temporary or permanent functional disabilities or psychological disorders. It may lead to consequences up to coma or even death. Although it has a common use with the term traumatic brain injury, there are differences. Head trauma or head injury; covers all injuries of the head (such as scalp, skull, facial injuries, mouth injuries, fractures). In definition, a head injury does not merely mean a brain injury. Traumatic brain injury, on the other hand, describes the entire range of pathologies of the brain parenchyma and brain function by mechanical influences. Head injuries can be classified into open and closed ones. With open head trauma, it describes severe traumas after a complete tabular fracture of the cranial bones, in which the structures inside the dura mater protrude beyond the scalp. It can be seen with high-energy traumas such as firearm injuries, falls from a height, motor vehicle accidents. It carries a high risk of mortality and morbidity (13). In closed head injuries, skin integrity is preserved. There is no contact of air with intradural structures. Diffuse brain injury may also occur with it. According to the Glaskow coma score, head injuries can also be examined according to the severity of post-traumatic neuropathological findings:

- Severe head injuries (GCS: 3-8)
- Moderate head injuries (GCS: 9-13)
- Mild head injuries (GCS: 14-15)

In terms of morphological signs, head injuries are classified as follows:

- **Focal brain damage**
  - Contusion and Laceration of the cerebrum
  - Hemorrhage / hematoma
    - Epidural hemorrage
    - Subdural hemorrage
    - Subarachnoid hemorrhage
    - Intraparanchymal hemorrhages
- **Skull fractures**
    - Linear fractures
    - Collapse fractures
- **Diffuse cerebral injuries**
    - Diffuse axonal injury

Two types of head injuries are mentioned according to the type of trauma:

- **Penetrating Head Injuries**
    - Gunshot injuries
    - Others
- **Blunt Head Injuries**
    - High speed (falling from a height, motor vehicle accident)
    - Low speed (falling from the same level, syncope)

There are not enough comprehensive studies on the incidence of head trauma in the geriatric population in our country. Approximately more than 240,000 patients go to emergency departments for head injuries every year in the United States, and approximately more than 80,000 geriatric patients annually receive a diagnosis from emergency departments as a traumatic brain injury, 75% of whom require hospitalization. Most of the hospitalized patients require intensive care follow-up, in addition, 13% of them are mortal. While high falls are the most common cause of head trauma geriatric (in a study

conducted in Australia with 12.564 patients, this rate is seen 80%), motor vehicle accidents stand out as the second most common cause (13).

In Canada and the USA, about 8% of the geriatric population over the age of 65 are admitted to the emergency department every year due to a fall from a height, 25% of them are hospitalized (14). Approximately 80% of the geriatric population over the age of 65 with all head injuries admitted to the emergency department are mild head injuries, and moderate head injuries account for 10% (14). It is one of the most important reasons that make geriatric head injuries a problem due to its high mortality and being an important morbidity factor. According to WHO data, 83.7 deaths per 100,000 secondary to trauma are reported worldwide per year. In the European region, which also includes Turkey, this rate increases to 131.5 per 100,000. Traumatic brain injuries are responsible for about a third of these deaths (14).

THE APPROACH TO GERIATRIC HEAD TRAUMA PATIENT

First response to trauma patients should be started at the scene. Taking measures to reduce intracranial pressure so that the respiratory tract is kept open is of life-saving importance in preventing the hypoxic state of the brain. The patient should not be moved uncontrolledly and precautions should be taken against the possibility of spinal injuries. Injuries of the cervical spine can affect vital functions, while other vertebral injuries can lead to permanent disabilities. The procedures that should be applied to patients with geriatric head trauma before they arrive at the hospital; basic and advanced life support, spine immobilization and referral to the nearest emergency department will be provided. After the patient is taken from the trauma site to a safer place, an initial assessment (such as injury sites, state of consciousness), airway assessment, ventilation, bleeding control, and spinal immobilization should be performed. Basic life support should be provided if needed. Bleeding control should be ensured. Fluid support should be started by providing vascular path patency. Unconscious patients should be treated as if they have a neurotrauma. The spinous protrusions of the cervical, thoracic and lumbar vertebrae should be palpated by individual examination, the presence of tenderness should be investigated. As much as possible, the immobility of the body should be ensured until the patient is transferred to the emergency department (15). In

head trauma patients, the respiratory tract may be blocked due to tongue, pharyngeal and laryngeal soft tissues, blood, teeth, direct trauma. Endotracheal intubation in the early period can be life-saving. Care should be taken to keep the neck stable while intubation is performed, and a possible complication of cervical spine injury should not be caused.

Computed tomography, which allows the skull and brain to be examined effectively and quickly in a patient with a head injury, without harming the patient, has enabled early surgical and medical treatment, which has increased patient survival rates. Computed tomography has become the most preferred imaging method in the evaluation of head injury patients today due to its rapidity and effectiveness in making a diagnosis, and easy accessibility and lack of contraindications. Although brain tomography provides a definitive diagnosis of head injuries, the benefit of using it in all patients is being questioned. It has been proven in broad-based studies that only 0.1-0.3% of patients who undergo brain tomography in minor head injuries require surgical intervention. This has led to the need to set criteria for tomography. Today, anamnesis, physical examination, examination and neurological examination are used to establish these criteria. The New Orleans criteria created by Haydel et al. were established by evaluating approximately 1500 minor head trauma patients who had undergone brain tomography (15).

New Orleans Rules

Patients to whom these rules can be applied (Inclusion criteria)

- Age > 18
- With a GCS score of 15
- Loss of consciousness or amnesia and disorientation within 24 hours after multiple blunt head trauma

Brain Tomography should be performed if patients have at least one of the following criteria

- Age >60 and over
- Headache (diffuse or local)
- Vomit
- Alcohol or drug intoxication (alcohol intake determined at the level either clinically or by looking)

- short-term memory loss (permanent antregrade amnesia)
- Signs of trauma in the region above the clavicle (contusion, abrasion, laceration, deformity, signs of facial and skull bone fractures)
- Seizure (posttraumatic seizure or suspected seizure)

In a patient with signs of increased intracranial pressure, care should be taken to raise the head of the bed by 30 degrees, maintain the average arterial pressure above 90, adequate fluid replacement and arterial oxygenation. Anti-edema treatments should be started as a precaution against brain edema. Hyperventilation has no place in treatment, as it causes cerebral ischemia. In patients with severe traumatic brain injury, a prophylactic installation of anti-epileptic therapy may be planned to prevent epileptic attacks. Although the hospitalization and mortality rates of the geriatric patient group after head trauma are high compared to other age groups, the mortality rate for mild head injuries is at the level of 0.1%. The rate of trauma that will require surgical intervention is about 1%. The proportion of patients with abnormal brain tomography findings in geriatric patient groups is 8%. Multidisciplinary evaluation is required in the emergency department where the geriatric patient population is admitted due to head trauma. Surgical treatment or medical follow-up is decided according to conditions such as neurological and physical examination of the patient, brain tomography follow-up, hemodynamics, variability in neurological follow-up. As a result of these analyzes, 80 out of every 1000 elderly patients admitted to the hospital have pathological brain tomography findings and are hospitalized, 9 of them require surgical intervention, and 1 of them is mortal (14).

REFERENCES

1. World Health Organization. (2021). Men, Ageing and Health. Geneva: WorldHealthOrganization,1999.https://apps.who.int/iris/bitstream/handle/10665/66941/WHO_ NMH_NPH_01.2.pdf;jsessioni.
2. World Health Organization. (2015). World Report on Ageing and Health. Luxembourg
3. Singh, S., & Bajorek, B. (2014). Defining 'elderly' in clinical practice guidelines for pharmacotherapy. *Pharmacy practice*, *12*(4), 489. https://doi.org/10.4321/s1886-36552014000400007
4. Turkish Statistical Institute. (2015). Demographic data. (http://www.tuik.gov.tr/PreHaberBultenleri.do?id=21520)
5. Strange, G. R., Chen, E. H., & Sanders, A. B. (1992). Use of emergency departments by elderly patients: projections from a multicenter data base. *Annals of emergency medicine*, *21*(7), 819–824. https://doi.org/10.1016/s0196-0644(05)81028-5
6. Durukan, P., Çevik, Y., Yıldız, M. Evaluation of the elderly patients with abdominal pain in the emergency department. *Turk J Geriatr*. 28(3):111-4. https://doi.org/10.17343/sdutfd.953443
7. Unsal, A., Çevik, A., Metintas, S., et al. Emergency department visits by elder patients. *Turk j Geriatr*. 6(3):83-8.
8. Loğoğlu, A., Ayrık, C., Köse, A. et al. Analysis of non-traumatic elderly patient presentations to the emergency department. *Tr J Emerg Med*. 13(4):171-9.
9. Rutland-Brown, W., Langlois, JA., et al. Incidence of traumatic brain injury in the United States, *J Head Trauma Rehabil* 21:544-8.
10. Kay, A., Teasdale, G. Head injury in the United Kingdom. *World J Surg* 25:1210-20.
11. Karasu, A., Sabancı, PA., Cansever, T., et al. Epidemiological study in patients with head trauma, *National J of Trauma Emergency Surgery* 15(2):159-163.
12. Zimmerman, RA., Bilaniuk, LT., Gennarelli, T., et al. Cranial computed tomography indiagnosis and management of acute head trauma. *AJR Am J Roentgenol* 131:27-34.

13. Jennett, B. Epidemiology of Head Injury.*J Neurol Neurosurg Psychiatry* 60:362-369.

14. Maxwell, CA., Miller, RS., Dietrich, MS., et al. The aging of America: a comprehensive look at over 25,000 geriatric trauma admissions to United States hospitals. *Am Surg.* 81(6):630-6.

15. Haydel, MJ., Preston, CA., Mills, TJ., et al. Indications for computed tomography in patients with minor head injury. *N Engl J Med* 343: 100–05.

CHAPTER 20

ELIMINATION METHODS IN THE INTOXICATED PATIENTS

Res. Asst. Meryem BALCI[1]
Asst. Prof. Dr. Ali AYGUN[2]

[1] Ordu University, Faculty of Medicine, Department of Emergengy Medicine, Ordu, Turkey. meryemmbalci@hotmail.com. ORCID ID: 0000-0002-1656-0315
[2] Ordu University, Faculty of Medicine, Department of Emergengy Medicine, Ordu, Turkey. dr_aliaygun@hotmail.com. ORCID ID: 0000-0002-5190-1445

INTRODUCTION

Elimination is the removal of a substance from the body after biotransformation. The substances taken from outside are excreted in the body through urine, feces, lungs and secretions. In cases of poisoning with a limited number of methods, we can accelerate the removal of xenobiotics from the body by increasing the elimination. However, the use of these methods in clinical practice is limited and they are not used in all types of poisoning (Table 1,2).

Table 1. Corporeal (In-body) methods

Urinary alkalinization
Repeated dose activated charcoal
Forced diuresis
Metal chelation
Resins (Prussian blue, cholestyramine, colestipol, kayexalate)

Table 2. Extracorporeal (Extracorporeal) methods

Hemodialysis
Hemoperfusion
Hemofiltration
Peritoneal dialysis
Plasmapheresis, exchange transfusion
Continuous renal replacement therapies
Liver support tools
Extracorporeal membrane oxygenation (ECMO)
Cerebrospinal fluid Exchange

1.CORPOREAL (IN-BODY) METHOTS

1.1. Urinary Alkalinization

Urinary alkalization is a method based on alkalizing the acidic urine pH (pH:4-5) to increase the elimination of weakly acidic xenobiotics. The most commonly used poisonings with this method are Salicylates, Phenobarbital and Methotrexate. These weak acids become ionized at alkaline urine pH and are excreted in the urine without being reabsorbed by the renal tubules. In alkalinisation, intravenous sodium bicarbonate (1-2 mEq/kg rapid iv bolus and maintenance iv infusion) is administered to raise the target pH of the urine to

7-8. The areas where this method is most commonly used are Salicylates, Phenobarbital and Methotrexate. The most important points to consider at this time are; serum pH does not exceed 7.5, serum potassium level does not fall below 4 mEq/L[1.]

1.2. Forced Diuresis

Forced diuresis is a method that aims to increase renal excretion by expanding the volume with fluids such as normal saline and Ringer's lactate in poisoning. While volume expansion may improve glomerular filtration rate and cardiac output in patients with reduced extracellular fluid content, this effect may be reduced or even harmful in patients with normal volume status. Particular attention should be paid to pulmonary and cerebral edema for patients with normal volume status[2].

1.3. Repeated Dose Activated Charcoal

Repeated dose activated charcoal aims to increase total body clearance of a limited number of compounds. Elimination of drugs with small volumes of distribution (<1 liter/kg), low pKa, low binding affinity and prolonged elimination half-life after overdose is particularly likely to be enhanced. Activated charcoal is administered orally or through a nasogastric tube at a dose of 0.5 g/kg every 6 hours, a total of 4 times, in order to increase the elimination of agents entering the enterohepatic circulation, except for the decontamination method. Thus, activated charcoal inhibits the enterohepatic circulation of the drug or toxin, preventing it from re-mixing into the systemic circulation and lowering its serum concentration. In cases where repeated dose activated charcoal administration is indicated, there are mushroom poisonings containing Carbamazepine, Amitriptyline, Cyclosporine, Dapsone, Digitoxin, Nadolol, Nortriptyline, Phenobarbitals, Cyclopeptide. It should not be forgotten that any situation where activated charcoal application for decontamination is contraindicated is also valid for repeated dose activated charcoal application[3,4]. Contraindications; suppression of consciousness without airway protection, risk and severity of aspiration, need for endoscopy, presentation with intestinal obstruction or reduced peristalsis, ingestion of toxins poorly absorbed by activated charcoal[5].

1.4. Metal Chelation

Heavy metals are elements such as lead, mercury, silver, cadmium, gold, cobalt, tin. Most heavy metals cannot be eliminated by the body's normal excretion pathways without special support. The most toxic heavy

metals are lead, cadmium, mercury and nickel. Classical chelation therapy is based on intravenous administration of EDTA (ethylene diamine tetra acetic acid) often together with vitamins B, C, magnesium and zinc. Once EDTA bound, these metals can be removed through the kidneys[6.] The application is done twice a week and this process takes an average of 2-3 hours. Rarely, chelation procedures can be done orally or by suppository, but the chances of success are not as effective as intravenous ones. However, IV chelation therapy is mostly aimed at acute toxications, and because it is an aggressive treatment, it may bind the minerals necessary for the body and cause them to be removed from the body.

2.EXTRACORPOREAL METHOTS

Extracorporeal methods represent the treatment group aimed at removing endogenous or exogenous poisons, supporting a vital organ. Its effectiveness depends on the physicochemical and pharmacokinetic properties of the xenobiotic. The extent to which the xenobiotic will be affected by the treatment is determined by its molecular size, protein binding, volume of distribution, water solubility and endogenous clearance.

Indications: exposure to poison that can be eliminated by extracorporeal therapy, poisoning with extractable drug/poison exceeding endogenous elimination, poisoning with high morbidity and mortality and no response despite all treatments, disruption of the moral metabolism pathway of the drug/toxin, poisoning with drugs with delayed effects , serious intoxications[5.]

2.1. Hemodialysis

Hemodialysis has been used clinically for more than 100 years since its discovery and is the most commonly used extracorporeal treatment for poisoning. Because hemodialysis is used for supportive treatment such as removing the toxin from the circulation, rapid correction of acid-base and electrolyte disorders, and reducing the volume load with ultrafiltration in cases with impaired renal function. During classical hemodialysis, blood and countercurrent dialysate are separated by a semipermeable membrane (dialyzer). Xenobiotics then diffuse across the membrane from the blood to the dialysate on a concentration difference basis. Blood is pumped through one lumen of a temporary dialysis catheter, passed through the machine, and returned to the venous circulation through the second lumen. In order for a substance to be removed from the blood by hemodialysis, it must have a small molecular weight (<10,000 Da), a low virtual volume of distribution (Vd<1), a hydrophilic structure, and a low protein binding ratio (<80%)[7]. The main

acute poisonings in which it is very effective in the management of Toxic Alcohols (Methanol, Ethylene glycol), Salicylates, Lithium, metformin, phenytoin, Valproic acid, Carbamazepine, Barbiturates and Massive Paracetamol poisoning**.**

In cases where hemodialysis is indicated, emergency nephrology consultation, rapid placement of the dialysis catheter and taking the patient to dialysis as soon as possible are of great importance in terms of morbidity, mortality and prognosis. Especially in critical situations where irreversible damage is expected such as toxic alcohol poisoning, dialysis should be applied as soon as possible after the indication. In poisoned patients, the average duration of hemodialysis is 4 hours. However, in cases where the toxin load is high, either the time is extended or the hemodialysis session is repeated after a short time. With the routine use of high-flux membranes, hemodialysis is as effective as hemoperfusion for eliminating certain xenobiotics. The undesirable effect of hemodialysis is that it removes the drugs and antidotes given for treatment purposes from the circulation. Therefore, the doses of these agents need to be increased during dialysis or re-administered immediately afterwards (Example: Ethanol, Fomepizole, N-acetylcysteine)[1]. It is contraindicated in patients who are hemodynamically unstable, with active bleeding, with severe thrombocytopenia or coagulopathy[5].

2.2. Hemoperfusion

Hemoperfusion is a hemodialysis-like method in which toxins are removed by passing blood through a catheter containing activated charcoal or resin with a very large absorbent surface area on which xenobiotics can be directly absorbed. Lipophilic substance intoxications are cleared to a lesser extent by hemodialysis or hemofiltration, because lipophilic substances exhibit high protein binding properties. Hemoperfusion is not limited to plasma protein binding. Hemoperfusion is preferred over hemodialysis for the removal of fat-soluble or highly protein-bound chemicals. Water and lipid soluble substances with molecular weights ranging from 113 to 40000 Da can be adsorbed. retained by activated charcoal so that a substance can be removed from the blood by hemoperfusion, molecular weight <40 KDa, small volume of distribution, unicompartmental kinetics, slightly-highly binding to plasma proteins, soluble in water or fat, low endogenous clearance (<4 mL/min per kg) must[5]. In most poisonings, 4-6 hours of treatment is sufficient to reverse the symptoms and signs of poisoning and to reduce serum levels to

a safe range. Compared with hemodialysis, patients need to be anticoagulated with a larger amount of heparin during the procedure. In addition, hemoperfusion has complications such as thrombocytopenia, leukopenia and hypocalcemia. Compared to the cost of the high-flow hemodialysis membrane, hemoperfusion cartridges are very expensive and not available in most clinics. Therefore, these limitations make the use of hemoperfusion less attractive compared to hemodialysis. Although hemoperfusion has historically been considered the method of choice to increase the elimination of carbamazepine, phenobarbital, phenytoin, and theophylline, old comparisons of hemodialysis and hemoperfusion clearance rates are no longer valid[8]. Currently, available evidence shows that high-flow hemodialysis has similar efficacy to charcoal hemoperfusion. High-flow hemodialysis has replaced hemoperfusion in clinical practice as the preferred treatment modality due to its potential efficacy, availability, lower cost and side-effect profile[3]. It is contraindicated in patients who are hemodynamically unstable, with active bleeding, with severe thrombocytopenia or coagulopathy[5].

2.3. Hemofiltration

Hemofiltration is the movement of plasma across a semipermeable membrane in response to an active hydrostatic pressure by convection. In pure hemofiltration, there is no dialysate solution on the other side of the dialysis membrane. Molecules are transported across the membrane by plasma water, a mechanism known as convective transport or bulk flow. Compared to hemodialysis (diffusion), hemofiltration facilitates the elimination of larger substances (eg myoglobin, molecular weight = 17,000 Da), but its effectiveness is limited for the elimination of smaller molecules. Since most substances of clinical importance in toxicology have a molecular weight of less than 1,000 Da, the use of hemofiltration in the management of patients presenting with poisoning is limited and has no specific indication that is considered superior to hemodialysis[3,7].

2.4. Continuous Renal Replacement Therapies

The term continuous renal replacement therapy (CRRT) is used to describe any continuous method of hemofiltration. Continuous venovenous hemofiltration (SVVHF) is the most commonly used dialysis with convective transport. Since the amount of blood flow in continuous renal replacement therapy (CRRT) is lower than that applied during intermittent techniques, the xenobiotic clearance that can be achieved is lower with this method. But SSRTs have a longer duration of administration (they can be done

continuously for several days). SSRTs are particularly suitable for hemodynamically unstable patients. It is recommended as an alternative therapy when intermittent hemodialysis is not available in severe poisoning with methanol, lithium, metformin. CRRT is a preferred method to eliminate a xenobiotic that is slowly dispersed from tissue binding sites or the intracellular compartment (For example, chronic lithium toxicity)[9]. Thus, as a result of rapid clearance of selected toxins from the serum, they are released from the tissues with a rebound effect and prevent them from reaching higher serum levels. However, since the rate and speed of toxin removal with this method is considerably lower than the intermittent hemodialysis method, it is not an ideal method especially for situations where rapid removal of the toxin is required[1,3].

2.5. Plasmapheresis, Exchange Transfusion

Plasmapheresis and exchange transfusion aim to remove xenobiotics with very high molecular weight (>100,000 Da) or heavily bound to protein from the circulation. The level of evidence that both techniques affect the clinical course and prognosis of a patient poisoned by any agent is very low. In the literature, there is information in the form of case reports that plasmapheresis has been used in mushroom poisoning containing cyclopeptide, snake envenomation, thyroxine, vincristine, digital poisoning. Plasmapheresis is expensive and both methods expose patients to the risk of plasma or blood-borne infections. Exchange transfusion may be useful as an elimination-enhancing method in the medical management of young infants in whom hemodialysis is technically difficult or impossible (Example: salicylate and theophylline toxicity)[3].

2.6. Liver Support Tools

Liver assist devices or liver dialysis is a new concept for poisoning. These extracorporeal devices can eliminate protein-bound xenobiotics, but the level of evidence for their use in poisoning is limited to case reports only. These devices are of 3 types: Single pass albumin dialysis (SPAD), The Molecular Adsorbents Recirculation System (MARS) and Prometheus system. They are often used in patients with hepatic encephalopathy and liver failure, to save time for liver transplantation[1,3]. In toxicology, mostly paracetamol or cyclopeptide have been used in liver failure after mushroom poisoning. The disadvantages are that their clinical availability is low, they are very expensive, and the level of evidence for their efficacy is low.

2.7. Extracorporeal Membrane Oxygenation (ECMO)

Although ECMO does not facilitate venom removal, it is used as a bridge to recovery in patients with clinically refractory cardiovascular and/or pulmonary failure who do not respond to conventional medical treatments. It is called venovenous ECMO (VV ECMO) providing only pulmonary support, and venoarterial ECMO (VA ECMO) providing pulmonary and circulatory support. VA ECMO is used to support patients with cardiovascular toxicity from calcium channel or beta blockers. VV ECMO provides pulmonary support to patients from inhaled organic hydrocarbons. It is also used successfully in various drugs such as tricyclic antidepressants, carbamazepine and chloroquine[5].

2.8. Cerebrospinal Fluid Exchange

Cerebrospinal fluid (CSF) exchange is occasionally performed in some patients with threatening neurological symptoms after certain poisonings, particularly after therapeutic errors following intrathecal administration. CSF is passively drained through a ventricular catheter and replaced with a sterile solution containing albumin and sodium chloride in the lumbar subarcnoid space. Most reported cases involve methotrexate poisoning[5].

REFERENCES

1. Olson K.R., & Anderson I.B., & Benowitz N.L., & Blanc P.D., & Clark R.F., & Kearney T.E., & Kim-Katz S.Y., & Wu A.B.(Eds.), (2018). *Poisoning & drug overdose, 7e*. McGraw Hill.
2. Calello D.P., & Henretig F.M. (2019). Lead. Nelson L.S., & Howland M, & Lewin N.A., & Smith S.W., & Goldfrank L.R., & Hoffman R.S.(Eds.), *Goldfrank's toxicologic emergencies, 11e*. McGraw Hill.
3. Goldfarb D.S., & Ghannoum M (2015). Principles and techniques applied to enhance elimination. Hoffman R.S., & Howland M, & Lewin N.A., & Nelson L.S., & Goldfrank L.R.(Eds.), *Goldfrank's toxicologic emergencies, 11e*. McGraw Hill.
4. Position statement and practice guidelines on the use of multi-dose activated charcoal in the treatment of acute poisoning. American academy of clinical toxicology; european association of poisons centres and clinical toxicologists. (1999). *Journal of toxicology. Clinical toxicology*, *37*(6), 731–751. https://doi.org/10.1081/clt-100102451
5. Gülen, B., & Taşlıdere, B. (2020). Clinical Toxicology in Emergency Medicine Practice.
6. Fulgenzi, A., Vietti, D., & Ferrero, M. E. (2020). EDTA chelation therapy in the treatment of neurodegenerative diseases: an update. *biomedicines, 8*(8),269. https://doi.org/10.3390/biomedicines80802690
7. Klaassen C.D.(Ed.), (2019). *Casarett & Doull's toxicology: the basic science of poisons, 9th edition*. McGraw Hill.
8. Ghannoum, M., Yates, C., Galvao, T. F., Sowinski, K. M., Vo, T. H., Coogan, A., Gosselin, S., Lavergne, V., Nolin, T. D., Hoffman, R. S., & EXTRIP workgroup (2014). Extracorporeal treatment for carbamazepine poisoning: systematic review and recommendations from the EXTRIP workgroup. *Clinical toxicology (Philadelphia, Pa.)*, *52*(10), 993–1004.
9. van Bommel, E. F., Kalmeijer, M. D., & Ponssen, H. H. (2000). Treatment of life-threatening lithium toxicity with high-volume continuous venovenous hemofiltration. *American journal of nephrology*, *20*(5), 408–411.

CHAPTER 23

APPROACH GASTROINTESTINAL BLEEDING

Res. Asst. Dr. Hamza Enes GÜÇLÜ[1]
Dr. Esma BULUT[2]

[1] Yozgat Bozok University, Faculty of Medicine, Department of Emergency Medicine, Yozgat, Türkiye, h.enes.guclu@yobu.edu.tr, Orcid ID: 0000-0003-2989-993X
[2] Yozgat Bozok University, Faculty of Medicine, Department of Emergency Medicine, Yozgat, Türkiye, E-mail: ozdarendeliesma@gmail.com, Orcid ID: 0000-0002-5553-6676

1

1. UPPER GASTROINTESTINAL BLEEDINGS

1.1. Introduction

Upper gastrointestinal tract bleeding originates proximal to the ligament of Treitz. It is an important clinical process that threatens life. It is more common in elderly and male patients. (Barkun, Almadi et al. 2019). In the emergency department, it should be carefully evaluated with anamnesis, examination and diagnosis process. Patients usually present to the emergency department with blood or coffee bean-like vomit (hematemesis) and/or black stools (melena).

1.2. Pathophysiology

Peptic ulcer disease is the most common cause of upper gastrointestinal bleeding. (Sostres and Lanas 2011). These are gastric, duodenal, esophageal and stomal ulcers. Other common causes are erosive gastritis, esophagitis and duodenitis. Although rare, another cause that can be fatal is stomach and esophageal varices. Mallory-Weiss syndrome is bleeding secondary to longitudinal mucosal tears at the gastroesophageal junction.

Dieulafoy's lesions (arteries of the GI tract protruding from the submucosa), arteriovenous malformation, and malignancies are other causes of upper gastrointestinal bleeding. Significant bleeding from the ear, nose, and throat may also appear as gastrointestinal bleeding.

1.3. Diagnosis

1.3.1. Medical History

Patients with GI bleeding go to the emergency room; It may present with weakness, dizziness, burning in the stomach, abdominal pain, palpitations, fainting, feeling unwell, black or red stools and bloody vomiting.

Although the medical history is very important in determining the source of bleeding, it can sometimes be misleading. (Like a patient presenting with hematochezia being diagnosed with upper GI bleeding). Let's recall the classic presentation symptoms:

Hematemesis: Vomiting red, bloody or coffee grounds. Brown vomiting refers to lighter bleeding; bloody vomiting is a precursor of moderate or severe upper gastrointestinal bleeding.

Melena: It is expressed as tar-colored, black stools. Although it indicates a hemorrhage originating from the proximal of Treitz ligament at a high rate, it can also be seen in lower gastrointestinal tract hemorrhages (Cappell and Friedel 2008).

Hematochezia: It is cherry-bruised red bleeding in the stool. It is frequently seen from lower gastrointestinal bleeding.

Whether there is gastrointestinal bleeding in the medical history of the patients, and if so, the diagnosis and treatment process should be learned from the patient, patient relatives and electronic health data system. It should be kept in mind that patients with a history of upper gastrointestinal bleeding may experience rebleeding from the same lesion at a high rate (Sostres and Lanas 2011).

Medications used by the patient should be carefully reviewed. Patients using salicylates, glucocorticoids, NSAIDs, and anticoagulants are particularly at high risk for GI bleeding. (DiGregorio and Alvey 2021). On the other hand, the use of bismuth, iron, charcoal, and licorice can darken the stool and mimic GI bleeding. Patients with alcohol use, peptic ulcer disease, erosive gastritis and esophageal varices are another patient group that should be careful in terms of GI bleeding.

1.3.2 Diagnostic tests

Blood gas, complete blood count, serum biochemistry and coagulation tests should be studied in patients with a preliminary diagnosis of GI bleeding. In addition, considering the need for transfusion, it is important to request blood group and cross-match tests. blood gas; quick assessment of hemoglobin, base excess, and lactate; It allows us to interpret the severity of bleeding and ischemia. Bleeding increases cardiac and mesenteric ischemia. ECG and cardiac biomarker tests should definitely be requested in patients with chest pain, palpitations, shortness of breath, history of coronary artery disease and advanced age.

Although routine abdominal and chest radiographs are not recommended; In patients with abdominal pain and tenderness in abdominal examination, standing straight abdominal X-ray and chest X-ray would be appropriate to evaluate perforation. Nasogastric tube is an important step in diagnosis and treatment in patients with suspected upper GI bleeding. Absence of any features on nasogastric aspiration does not definitively exclude an upper GI hemorrhage.Physical Examination

The patient's vital signs should be evaluated and unstable patients should be followed from the resuscitation room. It should be noted that GI bleeding may occur below hypotension, tachycardia, angina, syncope, malaise, confusion, or cardiac arrest. Young and comorbid patients can tolerate significant volume loss with little or no change in vital values. β-blockers can

prevent tachycardia; Patients with hypertension may have relatively normal blood pressure in hypovolemia. Cool, moist skin is an obvious sign of shock. Petechiae and purpura suggest an underlying coagulation disorder. A careful ear, nose, and throat examination may reveal an occult source of bleeding that causes swallowing of blood followed by vomiting of coffee grounds. Abdominal examination may reveal tenderness, masses, ascites, or organomegaly. In the rectal examination, bright red, coffee grounds or black stools can be seen.

1.4. Treatment

Focus on stabilizing the patient. Unstable patients should be monitored immediately, wide lumen double vascular access should be established and oxygen support should be prepared when necessary (safety circle). Especially in patients with severe bleeding and unstable airway protection and volume replacement is the first priority. Considering the risk of hypotension and cardiac arrest during intubation of hemodynamically unstable patients, low-dose induction agents can be used (DiGregorio and Alvey 2021).

In severe bleeding, it is necessary to contact the blood bank early for the flowing transfusion and to ensure that the necessary preparations are made. The transfusion threshold was determined as 7 grams/dL of hemoglobin and 9 grams/dL in elderly patients with acute comorbidities (Villanueva, Colomo et al. 2013).

The gastroenterology department should be contacted by starting the treatment of hemodynamically stable patients. High-dose proton pump inhibitors are used in treatment to keep gastric pH normal (Bennett, Klingenberg et al. 2014). Administer an IV bolus of 80 milligrams, then resume maintenance therapy at 8 milligrams/hour. In addition, Octreotide, a somatostatin analog, can be used in patients with upper GI bleeding.

Endoscopy is the most important diagnostic method in GI bleeding. In most cases, it enables the identification of the source of bleeding and the administration of hemostatic therapy. Endoscopy is recommended within 6–24 hours of admission for unstable patients and within 12–36 hours for stable patients (Barkun, Almadi et al. 2019).

Balloon tamponade is recommended to refer patients to an appropriate institution and to remain stable until endoscopy can be performed. Surgical intervention is required for patients whose bleeding cannot be controlled after medical treatment and endoscopy.

1.5. Discharge:

Patients who are hemodynamically stable can be followed up in the service. Otherwise patients with severe bleeding are followed in intensive care units.

2. LOWER GASTROINTESTINAL BLEEDINGS

2.1. İntroduction

Lower gastrointestinal (GI) bleeding describes bleeding from the colon and rectum under Treitz ligamanthin. Lower GI bleeding is less common than upper GI bleeding. Its incidence is about 20/100,000 in society per a year. Patients which face with this ilness are generally at an older age and at a higher rate in the male sex(Cappell & Friedel, 2008).

2.2. Pathophysiology

The arrival of bright light red or cherry rot color from the rectum is called hemothexesia. Although it is usually caused by lower GI, it can be caused by upper GI and makes you think of rapid bleeding. Melena which is a black, slimy, foul-smelling stool is often the cause of upper GI hemorrhagic. However lower GI can also be seen in hemorrhage in slow bleeding, Etiologically, diverticulosis is most common in patients diagnosed with bleeding of the lower gastrointestinal tract, followed by hemorrhoids as angiodysplasia, infectious, ischemic, neoplastic causes and anorectal hemorrhage, respectively. Diverticullary which demonstrate bright red bleeding, cannot cause a pain (Gralnek, Neeman, & Strate, 2017)

2.3. Story-Physical Examination

Patients should be questioned for old GI bleeding anamnesis. Patients should be asked about a history of drug using [e.g. aspirin, nonsteroidal anti-inflammatory drug (NSAID), anticoagulant, antiaggregate] that will cause bleeding or coagulation disorder. The findings and complaints of the patients should be reviewed in detail. Patients may also have applications in the form of rest tachycardia, follow-up, orthostatic hypotension, decreased pulse pressure, syncope, angina, weakness. Cold, pale skin and capillary refill elongation may be a sign of shock.The history of pain in the abdomen, trauma in the abdomen, foreign body intake and recent colonoscopy are remarkable for history of ilness. The aortic patch story provides to consider the possibility of aortaenteric fistula(Farrell, Friedman, & therapeutics, 2005). Iron or bismuth intake which can be reflected like melena may also look like hematoxia in foods as beet. It should be examined deeply to provide hemodynamic stability. Petechi or purpura may suggest underlying coagulopathy. Sensitivity in the abdomen, masses, acid can be detected in the examination. The cause of bleeding such as laseration, mass, anal fissure or external hemorrhoids can be showed during

anorectal examination . A digital rectal examination is performed to find bleeding and mass.

2.4. Laboratory

Laboratory Tests which are full blood examination, biochemistry, kidney and liver enzymes should be studied with coagulation parameters (in terms of underlying liver disease).

An ECG is taken to diagnose ischemias secondary to reduced cardiac oxygenation, which accompanies pronounced bleeding.

2.5. Visualization

Direct X-ray is required for perforation, obstruction or foreign body equation. Colonoscopy, radionuclide imaging, CT angiography and angiography can be preferred as the main diagnostic method in lower GI bleeding evaluation.

The superiority of colonoscopy compared to other examinations can be listed as making more accurate determinations, predicting the probability of recurrence of bleeding, pathological parts can be removed and offering the option of intervention for treatment. The disadvantage of colonoscopy is that it does not give good results without intestinal preparation and the risks that sedation can pose. Colonoscopy should be planned within 24 hours after bleeding in high-risk cases(Jensen, Machicado, Jutabha, & Kovacs, 2000). Radionuclide scintigraphy, CT angiography and interventional angiography are available as other alternative diagnostic options. Radionuclide scintigraphy provides the detection of bleeding in small amounts such as 0.05 ml/min. It is most often used to determine the location of bleeding in patients with persistent bleeding and whose gastrointestinal endoscopy results normally. CT angiography gives the advantage of providing anatomical localization information to interventions to be performed, although not invasive. CT angiography has disadvantages in terms of iv contrast agent and radiation exposure(Olds et al., 2005).

2.6. Treatment

The patient should be monitored to provide hemodynamic stability. Oxygen support should be provided to the patient after nasal cannula should be preferred.Two wide vascular tracts should be opened quickly. Liquid replacement should be performed immediately in the intavenous way that opened. First choice may be serum physiological or ringer lactate. if the patient has coagulopathy,Full blood examination, biochemistry, kidney and liver enzymes and coagulation parameters (in terms of underlying liver disease)which comes from laboratory examinations should consider. The need for blood transfusions should be evaluated in cases with severe and active bleeding. The decision to donated blood should be based on clinical symptoms.

Blood transfusion can be described as vital signs and circulatory failure if the ongoing active bleeding continue and impregulation is at 2000 cc fluid infusion. The demand for blood transfusions occurs more frequently in the elder people (Cappell & Friedel, 2008). If the lower GI bleeding is evident, you should consider wearing a nasogastric tube. Colonoscopy is the first procedure for all patients presenting with acute lower GI bleeding symptoms. It is used diagnostically and therapeutically. injection sclerotherapy, electrocoagulation, band, heat probe application which are types of colonoscopic hemostasis methods in therapeutic forms help to stop active bleeding(Jensen et al., 2000).Emergency surgery may be required if active bleeding continues and endoscopic intervention is unsuccessful.

2.7.Discharge

Patients usually need hospitalization and early colonoscopy. Patients who are hemodynamically unstable or who continue to bleed require intensive care admission.

REFERENCES

Barkun, A. N., Almadi, M., Kuipers, E. J., Laine, L., Sung, J., Tse, F., ... & Bardou, M. (2019). Management of nonvariceal upper gastrointestinal bleeding: guideline recommendations from the International Consensus Group. *Annals of internal medicine*, *171*(11), 805-822.

Bennett, C., Klingenberg, S. L., Langholz, E., & Gluud, L. L. (2014). Tranexamic acid for upper gastrointestinal bleeding. *Cochrane Database of Systematic Reviews*, (11).

Cappell, M. S., & Friedel, D. (2008). Initial management of acute upper gastrointestinal bleeding: from initial evaluation up to gastrointestinal endoscopy. *Medical Clinics of North America*, *92*(3), 491-509.

DiGregorio, A. M., & Alvey, H. (2021). Gastrointestinal bleeding. In *StatPearls [internet]*. StatPearls Publishing.

Sostres, C., & Lanas, A. (2011). Epidemiology and demographics of upper gastrointestinal bleeding: prevalence, incidence, and mortality. *Gastrointestinal Endoscopy Clinics*, *21*(4), 567-581.

Villanueva, C., Colomo, A., Bosch, A., Concepción, M., Hernandez-Gea, V., Aracil, C., ... & Guarner, C. (2013). Transfusion strategies for acute upper gastrointestinal bleeding. *New England Journal of Medicine*, *368*(1), 11-21.

Farrell, J. J., & Friedman, L. S. (2005). the management of lower gastrointestinal bleeding. *Alimentary pharmacology & therapeutics*, *21*(11), 1281-1298.

Gralnek, I. M., Neeman, Z., & Strate, L. L. (2017). Acute lower gastrointestinal bleeding. *New England Journal of Medicine*, *376*(11), 1054-1063.

Jensen, D. M., Machicado, G. A., Jutabha, R., & Kovacs, T. O. (2000). Urgent colonoscopy for the diagnosis and treatment of severe diverticular hemorrhage. *New England Journal of Medicine*, *342*(2), 78-82.

Olds, G. D., Cooper, G. S., Chak, A., Sivak Jr, M. V., Chitale, A. A., & Wong, R. C. (2005). The yield of bleeding scans in acute lower gastrointestinal hemorrhage. *Journal of clinical gastroenterology*, *39*(4), 273-277.

CHAPTER 24

EMERGENCY APPROACH TO VERTİGO

Res. Asst. Dr. Deniz TANRIVERDİ[1]
Dr. Mustafa Said ACAR[2]

[1] Yozgat Bozok University , Faculty of Medicine , Department of Emergency Medicine, Yozgat , Türkiye. detan5561@gmail.com, Orcid ID: 0000-0001-9888-3558
[2] Yozgat Bozok University, Faculty of Medicine , Department of Emergency Medicine, Yozgat, Türkiye. acarmustafasaid@gmail.com, Orcid ID: 0000-0003-4369-2521

1.EMERGENCY APPROACH TO VERTİGO

Vertigo reflecting the disturbance of normal perception of balance is a very common and complex neurological symptom. Dizziness is categorized as a kind of syncope, unsteadiness, and vertigo; It is also a magic of movement, typically defined as the environment turning; a feeling of weakness or dizziness which is similar to syncope; here imbalance is a feeling of imbalance while walking and nonspecific vertigo is usually associated with a multisensory disorder with an anxiety component (Sloane, Linzer et al. 1991).

Acute vestibular syndrome is used to describe a kind of clinical conditions of which dizziness develops acutely, but is persistent, lasts longer than one day, and is accompanied by nausea or vomiting, unsteady gait, nystagmus, and intolerance to head movement. Although common causes of dizziness (such as benign paroxysmal positional vertigo [BPPV] and vestibular neuritis) are usually easily diagnosed with history and specific diagnostic tests, sometimes a definitive diagnosis is not always possible, even after imaging tests and neurology consultation (Hotson and Baloh 1998).

1.1. Pathophysiology

The end organs of the vestibular system, the semi-circular canals and the otolith organs, sense angular and linear motion, respectively. As a result, a patient's description of a spinning sensation is likely to indicate an abnormality of the semi-circular canals or the central nervous system structures that process signals from the semi-circular canals. Similarly, an illusory sensation of floating or tilting may indicate an otolith system disorder (Highstein, Fay et al. 2004).

Important to the pathogenesis of vertigo is the fact that there is a vestibular labyrinth on each side of the body. The central nervous system receives signals from both the right and left labyrinths and compares these signals with one another. When the head is still, tonic discharges in both vestibular afferents are exactly balanced. During motion, the right and left labyrinths are alternately excited and inhibited, leading to a left-right difference in eighth nerve activity, which is recognized as motion. (Valko, Lewis et al. 2012)

The semicircular canals provide information about motion and angular momentum, while the utricle (via otoliths, which are calcium carbonate particles attached to hairy cells) provide information about head tilt and linear acceleration. Sensory inputs entering from the vestibular apparatus travels to the nucleus of the eighth cranial nerve. Central nervous system (CNS) structures that combine input from this sensory modality include the medial

longitudinal fasciculus, red nucleus, parietal and superior temporal gyri of the cerebellum and cerebral cortex. The system is completed by the connections between these structures and the oculomotor core system organizing the vestibulo-ocular reflex (VOR). VOR prevents the problem of blurred vision caused by head and body movements. (Raphan and Cohen 2002)

Semicircular canals are paired, left and right ear, structures that normally respond symmetrically to movement. In inner ear disease, the discharge at rest or the discharge stimulated by movement may vary in one ear. This change produces asymmetrical responses and causes the perception of vertigo. For example, freely moving otoliths improperly positioned within semicircular canals, such as in BPPV, can produce positional vertigo as the otoliths move under the influence of gravity and signal that the head is spinning inappropriately while the head is not (Furman and Cass 1999).

The most important clinical symptom associated with dizziness is nystagmus. Nystagmus is the rhythmic movement of the eyes with fast and slow parts and named according to the direction of the fast part. The rapid part of the nystagmus is caused by the cortex. It occurs as a quick corrective action to the opposite part. When the affected side is placed in a fixed position, nystagmus due to vestibular damage or dysfunction is evoked and its characteristic pattern is vertical or horizontal with rotation. Vertical nystagmus alone, not associated with a rotational component, usually indicates a brain stalk pathology (Pierrot-Deseilligny and Milea 2005).

1.2. Clinical Features

Vertigo is often classified in two groups as “peripheral” or “central”. Peripheral dizziness is caused by conditions affecting on the vestibular system and the eighth cranial nerve. Central vertigo is due to the disorders affecting central structures such as the brain stalk and cerebellum. Vertigo is presentation with nausea, vomiting and sweating. As for, peripheral vertigo is not associated with changes in mentality or with syncope (Bisdorff, Von Brevern et al. 2009).

The onset and duration of dizziness are important clues to the cause of dizziness. For example, episodic vertigo lasting less than one minute, primarily with repositioning, is suggestive of BPPV. A patient with BPPV usually feels dizzy at every head movement (Lempert and von Brevern 2005).

1.3. Diagnosis

1.3.1. History

In the diagnosis of the disease, as a first step, it should be determined whether the dizziness is peripheral or central. The symptoms of central vertigo,

although not severe, are more potentially life-threatening. Peripheral vertigo is more severe than central vertigo and is more associated with photophobia, hearing loss, tinnitus, sweating, nausea, and vomiting. On the other hand, central vertigo is more associated with neurological signs and symptoms such as diplopia, slurred speech, and bilateral visual impairment (Paul, Simoni et al. 2013).

Patients with vertigo should undergo ear examination, neurological and vestibular examinations. Dizziness with nystagmus caused by the introduction of air using a pneumatic otoscope is diagnostic for inner ear fistulas.

Nystagmus is the most important sign of dizziness. Abnormal nystagmus is the main manifestation of inner ear disease and the main sign of abnormal vestibular function. Positional nystagmus induced by repositioning the head is strongly suggestive of the presence of an organic vestibular disorder, typically BPPV. The diagnosis of BPPBD involving the posterior canal is done with the aid of the Dix-Hallpike position test. This test should not be performed in case of the risk or possibility of cervical spondylosis, spinal cord injury, vertebrobasilar insufficiency (VBI), cerebrovascular disease. The diagnosis of BPPBD involving the posterior canal is done with the aid of the Dix Hallpike test. This test should not be performed in case of the risk or possibility of cervical spondylosis, spinal cord injury, vertebrobasilar insufficiency (VBI), cerebrovascular disease. At all stages of the test, patients as eyes open should investigate the nose or forehead of the examining physician (Viirre, Purcell et al. 2005).

In the starting position, the patient should sit upright on the stretcher. In addition, the patient should be close to the head of the stretcher so that when stretched, the head should be able to extend backwards and be angled down 30 to 45 degrees in addition. In this way, the head keeping in a 20-degree lower position, it should suddenly be brought back to the natural position. Cyclic nystagmus after a pause of not more than 30 seconds is considered positive. Nystagmus exhibits rapid eye jerks in the direction of the affected ear and lasts 10-40 seconds. The patient is then returned to the sitting upright position. this test will be repeated for the left side. The direction in which the test is positive is the direction of the lesion.

The presence of cranial nerve deficits indicates a lesion occupying in the brain stalk or cerebellopontine angle, such as an acoustic neuroma. Cerebellar function is performed by using several test techniques. Dysmetria is the inability to control the distance, speed, and range of motion necessary to perform smoothly coordinated movements (Schmahmann 2004). Dysmetria is

a sign of cerebellar damage, and often presents along with additional signs, such as loss of balance and poor coordination of walking, speech, and eye movements. More specifically, dysmetria is a type of cerebellar ataxia, which is the general term used to describe an abnormal coordination of movements.

Patients with central vertigo usually cannot stand or walking without helping. The primary features of cerebellar gait are instability, irregular stride, trembling in the trunk, and swaying from side to side. Instability is most evident when quickly rising from a sitting position, turning rapidly, or stopping suddenly while walking. In addition, patients with gait ataxia cannot perform the heel-to-toe walking.

1.3.2. Imaging

Risk factors may help decide which patients require imaging. For patients causes of vertigo, advanced age, male gender, hypertension, coronary artery disease, diabetes, and atrial fibrillation are higher risk groups. Urgent brain CT or MRI is indicated, when cerebellar haemorrhage, cerebellar infarction, or other central lesions are suspected. MR is the diagnostic method of choice for lesions of the posterior fossa as well as for rare causes of vertigo (Edlow, Gurley et al. 2018).

1.4. Treatment

In general, short-term drug therapy is the main treatment in patients with peripheral vertigo. The goals of drug therapy are to reduce dizziness, assist in vestibular recovery, and relieve accompanying symptoms such as nausea, vomiting, and anxiety (Rascol, Hain et al. 1995).

REFERENCES

Park, J. H., & Kim, J. S. (2013). Classification of Vestibular Symptoms: Towards an International Classification of Vestibular Disorders. *Research in Vestibular Science*, *12*, S49-S52.

Park, J. H., & Kim, J. S. (2013). Classification of Vestibular Symptoms: Towards an International Classification of Vestibular Disorders. *Research in Vestibular Science*, *12*, S49-S52.

Furman, J. M., & Cass, S. P. (1999). Benign paroxysmal positional vertigo. *New England Journal of Medicine*, *341*(21), 1590-1596.

Highstein, S. M. (2004). Anatomy and physiology of the central and peripheral vestibular system: overview. *The vestibular system*, 1-10.

Hotson, J. R., & Baloh, R. W. (1998). Acute vestibular syndrome. *New England Journal of Medicine*, *339*(10), 680-685.

Lempert, T., & von Brevern, M. (2005). Episodic vertigo. *Current opinion in neurology*, *18*(1), 5-9.

Paul, N. L., Simoni, M., & Rothwell, P. M. (2013). Transient isolated brainstem symptoms preceding posterior circulation stroke: a population-based study. *The Lancet Neurology*, *12*(1), 65-71.

Pierrot-Deseilligny, C., & Milea, D. (2005). Vertical nystagmus: clinical facts and hypotheses. *Brain*, *128*(6), 1237-1246.

Raphan, T., & Cohen, B. (2002). The vestibulo-ocular reflex in three dimensions. *Experimental brain research*, *145*(1), 1-27.

Rascol, O., Hain, T. C., Brefel, C., Benazet, M., Clanet, M., & Montastruc, J. L. (1995). Antivertigo medications and drug-induced vertigo. *Drugs*, *50*(5), 777-791.

Schmahmann, J. D. (2004). Disorders of the cerebellum: ataxia, dysmetria of thought, and the cerebellar cognitive affective syndrome. *The Journal of neuropsychiatry and clinical neurosciences*, *16*(3), 367-378.

Sloane, P. D., Linzer, M., Pontinen, M., & Divine, G. W. (1991). Clinical significance of a dizziness history in medical patients with syncope. *Archives of internal medicine*, *151*(8), 1625-1628.

Valko, Y., Lewis, R. F., Priesol, A. J., & Merfeld, D. M. (2012). Vestibular labyrinth contributions to human whole-body motion discrimination. *Journal of Neuroscience*, *32*(39), 13537-13542.

Viirre, E., Purcell, I., & Baloh, R. W. (2005). The Dix-Hallpike Test and The Canalith Repositioning Maneuver. *The Laryngoscope*, *115*(1), 184-187.

CHAPTER 25

ORGANOPHOSPHATE (OP) POISONING AND EMERGENCY MANAGEMENT

Assoc. Prof. Dr. İbrahim ÇALTEKİN[1]

[1] Ordu University, Faculty of Medicine, Emergency Department, Ordu, Türkiye. dr.i.caltekin@gmail.com, Orcid ID: 0000-0002-3973-0655

INTRODUCTION

Insecticides are compounds and related species used to kill insects. Organophosphate (OP) insecticides are chemical insecticidal agents that have been widely used in agriculture, horticulture and veterinary fields since the 1970s. Some (eg malathion) are used to treat agents such as scabies and lice. OP nerve agents have also been used in warfare and terrorist attacks (Vale & Lotti, 2015).

The mortality rate of poisoning due to organophosphate ingestion is quite high, and deaths are usually the result of delayed or inappropriate treatment. More than 100,000 people in the world are poisoned with these compounds every year. Due to their easy availability, they are frequently used for suicide purposes, especially in rural areas or by people engaged in agriculture. About 30% of suicide attempts result in death.

It is one of the most common causes of poisoning in developing countries such as Turkey. Poisoning is also common in farm workers and children. It is at the forefront of poisonings that require intensive care treatment (Kwong, 2002; Sungur & Güven, 2001).

The two main groups of insecticide pesticides commonly used are organophosphates and carbamates. Organophosphate insecticides act as irreversible cholinesterase inhibitors, while carbamates act as reversible cholinesterase inhibitors. This is the main reason why central nervous system (CNS) symptoms are more prominent in OP poisoning (Tafuri & Roberts, 1987).

1. OVERVIEW OF ORGANOPHOSPHATE (OP) POISONING

Poisoning with OP is an important cause of morbidity and mortality in young and economically active age groups with low education and socioeconomic levels, especially in developing countries. OP is absorbed into the body through mouth, respiration, skin and eyes. They are rapidly distributed to all tissues, especially they accumulate in adipose tissue, liver and kidney. The severity of OP poisoning depends on factors such as the type of OP exposed, the amount ingested, the route of exposure, the rate of absorption, the rate of metabolic degradation, and the history of prior exposure to cholinesterase inhibitors. After Organophosphate compounds (OPCs) enter the

body and are absorbed, they bind covalently to phosphate radicals in the active site of acetylcholinesterase (AChE) in CNS and erythrocytes and butyrylcholinesterase in plasma, thereby irreversibly inhibiting these enzymes. Acetylcholine (Ach), which is not hydrolyzed and accumulates as a result of the inhibition of these enzymes, creates symptoms of poisoning by overstimulation of cholinergic receptors (Tunçok & Hocaoğlu, 2006).

2. SYMPTOMS AND SIGNS DUE TO ORGANOPHOSPHATE (OP) POISONING

Signs and symptoms of organophosphate poisoning depend on the balance between nicotinic and muscarinic receptors. These findings are shown in Table 1 (Reji et al., 2016; Tunçok & Hocaoğlu, 2006).

Effect mechanism	**Signs and symptoms**
1. Muscarinic receptor stimulation	Diarrhea, increased urine output, miosis, increased bronchial secretion, bronchospasm, bradycardia, nausea, vomiting, increased lacrimation, increased salivation.
2. Nicotinic receptor stimulation	Weakness, tachycardia, hypertension, hyperglycemia, muscle weakness, fasciculations, respiratory muscle paralysis, mydriasis.
3. Central nervous system	Headache, fatigue, tremor, ataxia, psychosis, delirium, seizure, respiratory system suppression, "intermediate syndrome" (weakness in neck flexor muscles, proximal arm and leg muscles, paralysis of motor cranial nerves and respiratory failure), delayed neuropathy.

3. DIAGNOSIS

In OP poisoning, the diagnosis is made by evaluating the signs and symptoms together with the history. Measuring suppression of plasma pseudocholinesterase (PChE) or erythrocyte AChE activity are laboratory

methods used to support the diagnosis (Tunçok & Hocaoğlu, 2006). The severity of clinical signs and symptoms often parallels the suppression of AChE activity, but this rule is not always valid according to the chemical structure of the organophosphate compound. In acute poisoning, if AChE activity is 20-50% mild, 10-20% moderate, and less than 10% severe poisoning symptoms occur (Clark, 2002).

4. EMERGENCY MANAGEMENT

The emergency treatment management consists of airway control, intensive respiratory support, general supportive measures, decontamination, prevention of absorption and antidote treatments. Organophosphate toxicity may vary from isolated gastrointestinal involvement to fulminant respiratory failure. The most important point of stabilization is to provide adequate oxygenation and ventilation. Patients should be given oxygen, cardiac monitoring and pulse oximetry should be fitted. In patients with excessive airway secretion and bronchospasm, giving 100% oxygen with a non-rebreathing mask reduces the risk of developing ventricular rhythm disorders during antidote therapy. However, gentle aspiration helps to clear airway secretions due to hypersalivation, bronchorea or vomiting. Coma, seizures, respiratory failure, increased respiratory secretions, severe bronchospasm require endotracheal intubation. In those with severe bronchospasm, dark secretions, or respiratory muscle weakness, emergency intubation and ventilation is indicated until the antidote is effective (Carey, Dunn, & Gaspari, 2013).

When neuromuscular blockade is required, a non-depolarizing agent should be used. Since succinylcholine is metabolized by plasma cholinesterase, it may result in a prolonged period of paralysis. Blood should be drawn for serum cholinesterase measurement. Hypotension should be treated primarily with isotonic crystalloid boluses. Bolus crystalloids at doses of 10-20 ml/kg are sufficient (Yurumez et al., 2007).

4.1. Prevention of Absorption

Gastric lavage is widely used after organophosphate intakes, especially in Asia, although there is no supporting evidence that it causes good results. Sometimes the symptoms appear quickly after ingestion, the benefit of gastric lavage is not much in patients who take large amounts and do not apply within

2 hours. The use of activated charcoal is sometimes recommended as it provides in vitro binding of organophosphate, but there is insufficient evidence for the outcome of single or multiple doses of activated charcoal to patients (Eddleston et al., 2008).

4.2. Organophosphate Decontamination

Secondary contamination of healthcare workers should be avoided during patient resuscitation. Neoprene or nitrided gloves should be preferred to latex gloves. Protective clothing and gloves should be worn. Patients with suspected poisoning should be removed from the contaminated environment. All clothing and accessories should be removed quickly, placed in a plastic bag and disposed of as hazardous waste. The patient should be decontaminated with plenty of soapy water and washed afterwards with diluted ethanol, if possible. The patient's skin should be quickly decontaminated with a mild detergent and water. Decontamination should include the scalp, hair, nails, skin, conjunctiva, and skin folds. If body fluids are contaminated, they should be treated. Irritation and abrasion of the skin should be avoided. Contaminated wastewater must be disposed of like hazardous materials. Contaminated tools should be cleaned with chlorine bleach (Alozi & Rawas-Qalaji, 2020).

4.3. Antidote Treatment

Specific antidote therapy should be initiated rapidly with basic supportive treatments. Specific antidotes used in OP poisoning are atropine and oximes (Eddleston & Chowdhury, 2016).

Atropine: Atropine, an antimuscarinic drug, is the main antidote with proven efficacy in OP poisoning. In OP poisoning, it is useful in antagonizing the cholinergic manifestations caused by the accumulation of ACh and over-stimulation of cholinergic receptors (Tunçok & Hocaoğlu, 2006).

Oximes (pralidoxim, obidoxim): It is the reactivator of the AChE enzyme inhibited by OP. However, the covalent bond formed between the OP and the AChE enzyme becomes stronger (aging) over time and an irreversible

inhibition occurs. Therefore, in OP poisonings, it is recommended to administer oximes within the first 24-48 hours before the irreversible enzyme phosphorylation called "aging" (Sarıtaş, Çakır, & Aslan, 2007).

While seizures in organophosphate poisonings are treated with airway manipulation, benzodiazepines and antidotes; pulmonary edema and bronchospasm are treated with oxygen, intubation, positive pressure ventilation, atropine and pralidoxime (PAM). Treatment of dysrhythmias is based on basic cardiac support criteria. Succinylcholine, ester anesthetics and beta-blockers should be avoided in possible poisoning (Tunçok & Hocaoğlu, 2006). In a prospective clinical study conducted in our country, it was determined that fresh frozen plasma (FFP) given in addition to atropine and PAM treatment in OP poisoning reduced the rate of development of "intermediate syndrome" and mortality. It has been determined that FFP can be an alternative treatment method in the treatment of OP, and it is stated that these findings should be supported by randomized controlled clinical and animal studies (Güven, Sungur, Eser, Sarı, & Altuntaş, 2004).

CONCLUSION

In conclusion, it should not be forgotten that OP agents, which are widely used as an insecticide, cause exposures that result in serious mortality and morbidity. However, respiratory failure secondary to paralysis of respiratory muscles and CNS depression are the most common causes of death (Sarıtaş et al., 2007; Tunçok & Hocaoğlu, 2006). These exposures lead to results that are difficult to treat and sometimes impossible.

REFERENCES

Alozi, M., & Rawas-Qalaji, M. (2020). Treating organophosphates poisoning: management challenges and potential solutions. *Critical reviews in toxicology, 50*(9), 764-779.

Carey, J. L., Dunn, C., & Gaspari, R. J. (2013). Central respiratory failure during acute organophosphate poisoning. *Respiratory physiology & neurobiology*, *189*(2), 403-410.

Clark, R. F. (2002). Insecticides: organic phosphorus compounds and carbamates. *Goldfrank's toxicologic emergencies, 8*, 1497-1512.

Eddleston, M., & Chowdhury, F. R. (2016). Pharmacological treatment of organophosphorus insecticide poisoning: the old and the (possible) new. *British journal of clinical pharmacology, 81*(3), 462-470.

Eddleston, M., Juszczak, E., Buckley, N. A., Senarathna, L., Mohamed, F., Dissanayake, W., . . . Jayamanne, S. (2008). Multiple-dose activated charcoal in acute self-poisoning: a randomised controlled trial. *The Lancet, 371*(9612), 579-587.

Güven, M., Sungur, M., Eser, B., Sarı, İ., & Altuntaş, F. (2004). The effects of fresh frozen plasma on cholinesterase levels and outcomes in patients with organophosphate poisoning. *Journal of Toxicology: Clinical Toxicology, 42*(5), 617-623.

Kwong, T. C. (2002). Organophosphate pesticides: biochemistry and clinical toxicology. *Therapeutic drug monitoring, 24*(1), 144-149.

Reji, K. K., Mathew, V., Zachariah, A., Patil, A. K. B., Hansdak, S. G., Ralph, R., & Peter, J. V. (2016). Extrapyramidal effects of acute organophosphate poisoning. *Clinical Toxicology, 54*(3), 259-265.

Sarıtaş, A., Çakır, Z., & Aslan, Ş. (2007). Organofosfat ve karbamat zehirlenmeleri. *The Eurasian J Med, 39*, 55-59.

Sungur, M., & Güven, M. (2001). Intensive care management of organophosphate insecticide poisoning. *Critical care, 5*(4), 1-5.

Tafuri, J., & Roberts, J. (1987). Organophosphate poisoning. *Annals of emergency medicine, 16*(2), 193-202.

Tunçok, Y., & Hocaoğlu, A. (2006). Organofosfatlı insektisitlerle zehirlenme. *Türkiye Klinikleri Cerrahi Tıp Bilimleri Acil Tıp Dergisi, 2*, 69-73.

Vale, A., & Lotti, M. (2015). Organophosphorus and carbamate insecticide poisoning. *Handbook of clinical neurology*, *131*, 149-168.

Yurumez, Y., Durukan, P., Yavuz, Y., Ikizceli, I., Avsarogullari, L., Ozkan, S., . . . Ozdemir, C. (2007). Acute organophosphate poisoning in university hospital emergency room patients. *Internal medicine*, *46*(13), 965-969.

CHAPTER 26

ANAPHYLAXIS AND TREATMENT

Dr. İsmail Kıvanç CEBECİOĞLU[1]

[1] Yozgat City Hospital, Emergency Department, Yozgat, Turkey
ki_vanc44@hotmail.com, Orcid ID: 0000-0002-8572-6200

INTRODUCTION

Anaphylaxis is a severe allergic reaction that occurs rapidly after contact with allergens. May produce hypotension, hypoxia, and airway edema as a result of histamine discharge, which can be potentially fatal (Sampson et al., 2006).

It is usually caused by an allergic reaction, but it can also be non-allergic. The clinic can range from mild symptoms such as a simple urticaria to life-threatening reactions including hypotensive shock. Delay in treatment is associated with increased morbidity and mortality (Nowak et al., 2013). Since it can be encountered frequently in places where all kinds of drug administration are performed, especially in emergency departments, its diagnosis and treatment should be well known by all emergency workers (Eren, Korkmaz, Güven, & Döles, 2010).

Although the exact incidence of anaphylaxis is not known, there are many publications on this subject. Medications, diagnostic substances and foods are the most common causes of anaphylaxis. The severity and incidence of anaphylaxis can be reduced with preventive approaches (Demirsoy, 2005).

Death due to anaphylaxis is due to circulatory collapse and respiratory arrest. There is no test to diagnose anaphylaxis and predict its outcome. While nutritional foods are usually the cause of anaphylaxis in children, drugs and insect bites are the main causes of anaphylaxis in adults (Demirsoy, 2005).

1. PATHOGENESIS

Although anaphylaxis has been known for over 100 years, its pathogenesis cannot be fully explained. Anaphylaxis that occurs with immunological mechanisms such as IgE, IgG or complement-mediated immune complexes is called "allergic anaphylaxis". Among these, those that occur through IgE are defined as "IgE-mediated allergic anaphylaxis", and those that occur with other immune mechanisms are defined as "non-IgE-mediated allergic anaphylaxis". Anaphylaxis that occurs by nonimmunological mechanisms is called nonallergic anaphylaxis, regardless of the cause (Bavbek, 2008).

Anaphylaxis that occurs by nonimmunological mechanisms is called nonallergic anaphylaxis, regardless of the cause (Bostancı & Doğru, 2011). These mediators are pre-synthesized mediators such as histamine, heparin,

tryptase, chymase, carboxypeptidase A3, tumor necrosis factor a (TNF-a), cathepsin G, and platelet activating factor (PAF), prostaglandin (PG) D2, leukotriene (LT) C4, cytokines (interleukin (IL) -5, IL-6, IL-8, IL-13, IL-33, TNF-a and granulocyte macrophage colony stimulating factor (GM-CSF) and chemokines (MIP-1a, MIP-1b) and there are two groups of newly synthesized mediators such as MCP1) (Bavbek, 2008; Bostancı & Doğru, 2011).

Rarely, mast cells and basophils can be immunologically stimulated without IgE mediation. IgG-mediated anaphylaxis has been reported due to high molecular weight iron dextran and infliximab. Complement-mediated anaphylaxis occurs in hemodialysis with heparin containing "oversulfated chondroitin sulfate" (OSCS), neutralization of heparin with protamine, in association with liposomal drugs and polyethylene glycol.

Anaphylaxis can also develop by non-immunological mechanisms. Physical factors such as exercise, cold, heat, sunlight/UV radiation, drugs such as ethanol and opiates may cause anaphylaxis by directly degranulating mast cells. There may be mediator release from mast cells without any cause (idiopathic). Some substances can cause anaphylaxis in more than one way. Heparin containing OSCS can cause anaphylaxis by both activating the complement system and activating the coagulation system. Radiocontrast agents also cause anaphylaxis, both IgE-mediated and non-IgE-mediated (Bostancı & Doğru, 2011).

2. CLINICAL FINDINGS

The signs and symptoms of anaphylaxis are highly variable. Findings can range from mild skin rash to fatal reaction (Karaman, Hocaoğlu, & Ölmez, 2006). If the antigen is administered by injection, symptoms usually appear within 5-30 minutes. If the antigen has been taken orally, it may take up to 2 hours for symptoms to appear. There are cases of anaphylaxis occurring hours after exposure to the antigen.

Hours after the attack has completely resolved, a new episode may begin, and this is called biphasic anaphylaxis. Biphasic anaphylaxis can be seen in 6% (Bavbek, 2008). It may develop on average 1.3-28.4 hours after the first symptoms have resolved. Sometimes, despite appropriate treatment, prolonged anaphylaxis with symptom-free hours but persisting for days can be observed. Prolonged anaphylaxis, which can be seen in 1%, has a high mortality rate

(2%). Biphasic anaphylaxis usually occurs in cases where adrenaline treatment is delayed, steroid treatment is not effective in preventing this situation (Bostancı & Doğru, 2011; Karaman, Hocaoğlu & Ölmez, 2006).

Skin: Itching, rash, urticaria, angioedema

Respiratory System: Stridor due to laryngeal obstruction, wheezing, cough, dyspnea, hypoxia and respiratory failure due to bronchospasm

Gastrointestinal System: Dysphagia, abdominal cramp, nausea, vomiting, diarrhea

Cardiovascular System: Arrhythmia, vascular collapse, hypotension

Neurological System: Dizziness, headache, syncope, convulsions, confusion, unconsciousness, diplopia, disorientation

Other Findings: Sweating, stool and urinary incontinence, death.

3. DİAGNOSIS

Anaphylaxis is highly likely if any of the following criteria are present (Oflu, 2015).

1- Sudden onset disease (minutes-hours) involving the skin, mucous membranes, or both (eg, generalized rash, itching or redness, swollen lips-tongue-uvula) and at least one of the following

a- Respiratory system involvement (eg, dyspnea, wheezing, bronchospasm, stridor, decrease in PEF, hypoxemia)
b- Symptoms associated with a fall in blood pressure or end organ dysfunction (eg, hypotonia, collapse, syncope, incontinence)

2- 2 or more of the side effects that develop rapidly after contact with a possible allergen
a- Involvement of skin-mucosal tissue (eg generalized rash, itching or redness, swollen lips-tongue-uvula)
b- Respiratory system involvement (eg, dyspnea, wheezing, bronchospasm, stridor, decrease in PEF, hypoxemia)
c- Symptoms associated with a fall in blood pressure or end organ dysfunction (eg, hypotonia, collapse, syncope, incontinence)

d- Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3- Decrease in blood pressure after contact with known allergen

a- Infants and children: Low systolic blood pressure (age specific) or more than 30% reduction in systolic blood pressure

b- Adult: Systolic blood pressure less than 90 mmHg or 30% less than the patient's baseline value

4. DIFFERENTIAL DIAGNOSIS

The differential diagnosis of anaphylaxis includes medical diseases of frequently affected organs (Bostancı & Doğru, 2011; Karaman, Hocaoğlu & Ölmez, 2006; Oflu, 2015).

Excessive endogenous histamine production: Mastocytosis and clonal mast cell diseases, Urticaria pigmentosa, Basophilic leukemia, Hydatid cyst, Rethionic acid-treated acute promyelocytic leukemia

Flush syndromes: Postmenopausal, Carcinoid syndrome, Autonomic epilepsy, Medullary thyroid carcinoma, Chlorpropamide, alcohol use, Red Man syndrome (Vancomycin), VIP and other vasoactive peptide secreting tumors.

Non-organic diseases: Vocal cord dysfunction, Munchausen syndrome

Shock: Hypovolemic, Cardiogenic, Endotoxic, Hypoglycemic

Postprandial syndromes: Pollen-food allergy syndrome, Scombroid fish poisoning, Ingestion of monosodium glutamate, Sulfites

Other: Pheochromocytoma, Idiopathic systemic capillary leak syndrome, Progesterone anaphylaxis, Non-allergic angioedema, Urticarial vasculitis, Hyper IgE urticaria syndrome.

5. TREATMENT

Because the diagnosis of anaphylaxis is not always clear, every physician treating anaphylaxis should use the systematic ABCDE (airway, respiratory, circulation, neurological status, Examination of the body) approach. All patients should be placed in a comfortable position. Patients with respiratory problems may prefer to sit (breathing becomes easier). Patients with hypotension should lie on their back with their legs elevated. Breathing and unconscious patients should be turned on their side (Kurtuluş, 2018)

Anaphylaxis treatment can be summarized as follows for the early and late stages of the event (Atakul, 2017; Bostancı & Doğru, 2011; Kurtuluş, 2018).

a. Early Intervention

- Airway, respiration, circulation, and consciousness should be evaluated.
- Epinephrine administration. 1/1000 epinephrine 0.2-0.5 mL (0.01 mg/kg to children, maximum 0.3 mg) should be given intramuscularly. This dose should be repeated at five-minute intervals according to symptom control and blood pressure. Intramuscular administration of 0.01 mg/kg results in rapid and high plasma levels. Since the delay in epinephrine will cause death, administration should be done on time.

b. Other Treatments Based on Epinephrine Response

- The patient's legs should be elevated.
- Airway clearance should be provided. For this purpose, face mask, ambu, endotracheal intubation and cricothyroidotomy are the methods to be used.
- Oxygen. In case of prolonged anaphylaxis, hypoxemia or myocardial dysfunction, oxygen therapy with pulse oximetry or blood gas monitoring should be administered.

- The vascular access should be opened and physiological saline support should be given. In the first five minutes, 5-10 mL/kg hydration should be applied.
- H1 and H2 antihistamines are supportive in the treatment of anaphylaxis. For the complaints of urticaria, angioedema and pruritus of anaphylaxis, 25-50 mg of diphenhydramine should be given by slow infusion in adults. The use of H2 antihistamines such as ranitidine and cimetidine is controversial, but co-administration of H1 and H2 antihistamines has been found to be more effective than H1 antihistamines alone. 50 mg of ranitidine in adults and 12.5-50 mg of ranitidine in children is the appropriate dose. The dose of cimetidine is 4 mg/kg intravenously in adults, and the pediatric dose is unknown.
- If bronchospasm persists despite epinephrine given in the early period, beta-agonist (nebulized albuterol, 2.5-5.0 mg) should be administered.
- Vasopressor drugs in cases where hypotension persists despite epinephrine and fluid loading. Under hemodynamic monitoring, dopamine infusion (400 mg dopamine 2-20 μg/kg/minute in 500 mL dextrose) should be given with a systolic pressure of 90 mmHg.
- For patients using beta-blockers, a glucagon infusion should be given. Intravenous glucagon at a dose of 1-5 mg (20-30 μg/kg/, maximum 1 mg in children) is administered slowly, 5-15 μg/minute infusion is appropriate if necessary, depending on clinical response.
- Steroids prevent prolongation or recurrence of anaphylaxis. Methylprednisolone 1-2 mg/kg/day intravenously every six hours, 0.5 mg/kg orally is recommended for milder anaphylaxis cases.
- Consideration should be given to transferring the patient to the emergency room or intensive care unit, if necessary.

6. LONG-TERM MONİTORİNG OF ANAPHYLAXİS

Most of the anaphylaxis attacks occur outside the hospital setting. For this reason, patients and/or those responsible for their care must know how to prevent the development of anaphylaxis, how to recognize it when it develops, and how to apply treatment. It is recommended that all patients diagnosed with

anaphylaxis be evaluated and monitored by allergy and clinical immunology specialists. Long-term follow-up of patients with anaphylaxis consists of protective measures and emergency preparation to reduce the risk of future attacks (Orhan et al., 2018).

Preventive measures to reduce anaphylaxis recurrence,

- Avoiding from the identified allergen/trigger
- Optimal management of cofactor and comorbid conditions
- Allergen-specific or non-specific immunomodulatory treatment methods (immunomodulation)

These preventive methods should be arranged for each patient by considering age, work, activity, hobby, social life and treatment needs.

REFERENCES

Atakul, G. (2017). Anafilaksi. *Klinik Tıp Pediatri Dergisi, 9*(1), 19-23.

Bavbek, S. (2008). Anafilaksi: Tanı ve Tedavi. *İç Hastalıkları Dergisi*, 15(1): 44-50.

Bostancı, İ., & Doğru, M. (2011). Anafilaksi ve anafilaksideki gelişmeler. *Çocuk Dergisi, 11*(2), 43-53.

Demirsoy, S. (2005). Anaflaksi. *Türkiye Klinikleri J Pediatr Sci, 1*, 1-12.

Eren, S. H., Korkmaz, İ., Güven, F. M. K., & Döles, K. A. (2010). Acil Serviste Dilalti Kaptoril Kullanilmasina Bagli Gelisen Anaflaksi/Anaphylaxis Due to Sublingual Captopril in Emergency Service. *Eurasian Journal of Emergency Medicine, 9*(4), 185.

Karaman, Ö., Hocaoğlu, A. B., & Ölmez, D. (2006). Anafilaksi nedenleri, tanısı ve tedavisi. *Güncel Pediatri, 4*(2), 8-12.

Kurtuluş, A. (2018). Derleme| Review. Anafilaksi | Anaphylaxis. *Güncel Göğüs Hastalıkları Serisi*, 6 (2): 157-160

Nowak, R., Farrar, J. R., Brenner, B. E., Lewis, L., Silverman, R. A., Emerman, C., . . . Miller, J. (2013). Customizing anaphylaxis guidelines for emergency medicine. *The Journal of emergency medicine, 45*(2), 299-306.

Oflu, A. T. (2015). Anafilaksi. *Kocatepe Tıp Dergisi, 16*(1), 77-82.

Orhan, F., Civelek, E., Şahiner, Ü. M., Arga, M., Can, D., Çalışkaner, A. Z., . . . Sarıçoban, H. (2018). Anaphylaxis: Turkish national guideline 2018. *Asthma Allergy Immunol*, 16(1), 1-62

Sampson, H. A., Muñoz-Furlong, A., Campbell, R. L., Adkinson Jr, N. F., Bock, S. A., Branum, A., . . . Galli, S. J. (2006). Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *Journal of Allergy and Clinical Immunology, 117*(2), 391-397.

CHAPTER 27

TOXIDROMES

Rahime Şahin TURAN[1]
Mesut TOMAKİN[2]
İhya OBRUKÇU[3]

[1] Ordu University Education and Research Hospital, Department of Emergency Medicine, Ordu, Türkiye. drrahime28@hotmail.com, Orcid ID: 0000-0002-8067-2944
[2]Ordu University Education and Research Hospital, Department of Emergency Medicine, Ordu, Türkiye. mesuttomakin@hotmail.com. Orcid ID: 0000-0002-7767-2177
[3]Ordu University Education and Research Hospital, Department of Emergency Medicine, Ordu, Türkiye. ihyaoprukcu@gmail.com, Orcid ID: 0000-0001-50968640

Toxidromes (Toxic Syndrome)

Toxidromes; these are clinical conditions that occur as a result of poisoning with toxic substances belonging to certain classes. It plays an important role in the diagnosis and grouping of poisonings. The causative agents of toxidromes generally have similar pharmacology.

As a result of poisoning, many effects occur in the organs. Among the affected organs, the most likely organ to be affected is the brain. The patient's unconsciousness leads to incomplete anamnesis. For this reason, it is very difficult and almost impossible to obtain information about the toxic agent in most poisonings. In order to solve this riddle in poisoned patients, it is necessary to bring to mind all the factors that are likely to poison the patient. Toxidromes have divided the patients into certain groups and thus guide us in patient management and treatment. In this way, it enables the effective and correct use of time in poisoning patients. Additionally; it sheds a great light on the detection of the agent causing poisoning and the revealing of the etiology.

Physical examination findings constitute the building blocks of toxidromes (toxic syndromes). To evaluate the patient in a particular toxidrome; a holistic approach is required, especially systemic examination findings and vital signs. Therefore, physical examination and findings are very important in acute poisoning patients. Especially, assessment of mental status, pupils, skin and mucous membranes, urinary retention or incontinence is important.

Toxidromes are mainly; divided into anticholinergic, cholinergic, sympathomimetic, opioid and hyperthermic. Hyperthermic toxic syndromes are subdivided into serotonin syndrome, neuroleptic malignant syndrome and malignant hyperthermia. The main signs and symptoms of toxidromes and toxidromes that are frequently encountered in the emergency department are shown in the table (Table 1) (1-2).

Table 1.Toxidromas and clinical findings

Toksidromes	**Clinical Findings**
Anticholinergic	Mydriasis, tachycardia, anhidrosis, delirium, urinary retention, decreased intestinal peristalsis
Cholinergic	Miyosis, bradycardia, bronchospasm, urinary incontinence, vomiting, diarrhea, lacrimation, salivation, cold sweats
Sympathomimetic	Mental deterioration, hypertension, tachycardia, tachypnea, hyperthermia, mydriasis, hyperreflexia, increased muscle tone, tremor
Opioid	Miyosis, somnolence, sedation, hyporeflexia, hypotension, bradycardia, decreased respiratory rate, decreased intestinal peristalsis
Sedative-Hypnotic	Mydriasis, agitation, hypertension, tachycardia, increased respiratory rate, hyperthermia, tremor, seizure, hyperreflexia
Serotonergic	Mental status change, hypotension, bradycardia, decreased respiratory rate, ataxia
Neuroleptic malignant syndrome	Hyperthermia, rigidity, autonomic instability, mental status change

1.Anticholinergic Toxidrome

Drugs and factors with anticholinergic effects competitively inhibit the binding of acetylcholine to muscarinic receptors and so show their effects. The effect of acetylcholine occurs through two different types of receptors, nicotinic and muscarinic receptors. Muscarinic receptors can exert their effects on the

circulatory system, respiratory system, gastrointestinal system, urinary system, eyes and skin, mainly through parasympathetic nerves in our body. Sweat glands innervated by sympathetic nerves are besides to stimulated by muscarinic receptors in addition to sympathetic system impulses. It is known that there are cholinergic pathways in the central nervous system, especially in regions related to memory and behavior. In patients poisoned in consequence of anticholinergic drugs or agents, symptoms and signs occur depending on the organs or systems in which muscarinic receptors or cholinergic pathways are present.

As the average life span of people increases, some health problems also increase with advancing age. Therefore, polymorphism is encountered especially in the geriatric patient group. Many drugs show their effects through the anticholinergic system. This situation increases the possibility of developing anticholinergic toxidroma according as drug abuse or misuse. In addition to routinely used and prescription drugs, many over-the-counter drugs can also show their effects through the anticholinergic system. Plants with alkaloid properties can be abused by humans for their hallucinogenic effects. Even if no abuse, excessive consumption of foods contaminated with such plants can also lead to anticholinergic toxidroma (4-5). Therefore, the clinician should act by considering every possibility in acute poisoning. It should not be forgotten that in order to make the diagnosis, it is necessary to suspect first. Some drugs and herbs known to cause anticholinergic toxidroma are summarized in Table 2 (3).

Table 2. Drug groups and derived plants

Drug Groups	**Plants**
Antiemetics	Belladona
Antiparkinson	Stramonyum
Gastrointestinal and Genitourinary Antispasmodics	Inoxia

Mydriatic and Cycloplegics	Albus
Antimigraine Drugs	Aureus
Antihistamines	Muticus
Antidiarrheals	Niger
Antiarrhythmics	Dulcamara
Skeletal Muscle Relaxants	Nigrum
Antidepressants	Suaveolens
Antipsychotics	Amanita Muscaria (fungus)

Clinical manifestations in anticholinergic toxidrome arise as a result of dysfunction of organs and systems stimulated by muscarinic receptors. The role of the clinician in the detection of these findings is great. If possible, anamnesis, vital signs, ECG and laboratory parameters of the patients should be evaluated by blending them with physical examination findings. Cognitive and memory disorders occur as a result of dysfunction in the central nervous system. Restlessness, anxiety, abnormal speech, confusion, agitation, tremor, ataxia, drowsiness, and coma may occur. Because of its effects on the eye, mydriasis occurs. Therefore, photophobia, loss of accommodation and impaired near vision may develop. Due to its effects on the circulatory system; An increase in systolic and diastolic blood pressure may occur. QRS enlargement may occur in the EKG as a result of poisoning with some drugs with anticholinergic effects such as diphenhydramine, cyclobenzaprine, carbamazepine and tricyclic antidepressants. Slowing of gastrointestinal motility due to dysfunction of the gastrointestinal tract, constipation or even an ileus table may develop due to this. Genitourinary system findings are usually in the direction of urinary retention. The mucous membranes become dry as a result of suppression of secretory cells. Skin dryness occurs in areas where muscarinic sweat glands are dense. This clinical finding is one of the findings that distinguishes

anticholinergic toxidrome from sympathomimetic toxidrome. Considering all these clinical signs and symptoms, for patients poisoned with anticholinergic drugs or agents; Dry as a bone, blind as a bat, red as a beet, hot as a rabbit, full as a flask and crazy crazy (6-8).

For the treatment of anticholinergic toxidrome, first of all, the patient should be evaluated and diagnosed. Then the treatment phase should begin with the initial evaluation. The basis of treatment is supportive therapy. Initially, the vitals of the patient should be evaluated and the patient stabilized. Airway patency should be established and maintained at the same time. Monitored follow-up of the patient is absolutely necessary. If the active substance is transmitted to the patient by contact, it should be removed from the body. Contacted areas must be cleaned. The body should be carefully examined, and if any, transdermal tapes should be removed. The patient should be evaluated for gastric lavage in short-term admissions after ingestion of large quantities. Activated charcoal should be evaluated for patients who have established airway patency and are able to preserve the airway. Activated charcoal may be beneficial in patients as anticholinergic agents are absorbed slowly from the gastrointestinal tract. It is recommended to apply activated charcoal at a dose of 1 g/kg. The superiority of single or multiple dose activated charcoal administration over each other has not been clearly demonstrated. In particular, the patient's agitation should be kept under control to prevent acidosis and rhabdomyolysis. It may even be necessary to restrain the patient physically. For agitation control, benzodiazepines are a suitable choice. Benzodiazepines should be given intravenously (IV) if possible. A slow IV infusion of 5-10 mg of diazepam can be administered to adult patients. In pediatric patients, diazepam 0.2-0.5 mg IV slow infusion can be administered. Lorazepam 2.5 mg IV can also be administered in agitated patients. Phenothiazines are contraindicated because of their anticholinergic effects. Although the indications for use are controversial, the use of physostigmine should be

considered in cases of hemodynamic instability. Since physostigmine crosses the blood brain barrier, it has both peripheral and central effects. It can cause an increase in cholinergic activity and related signs and symptoms may occur. Due to the toxic effects of physostigmine, it is recommended to be administered as a slow infusion over 5 minutes. It is recommended to administer 0.5-2 mg IV in adult patients and 0.02 mg/kg IV in pediatric patients. It can be repeated about 10 minutes apart until the patient is stable. The elimination of physostigmine in the body is about 1 hour. Therefore, the anticholinergic effects may reappear approximately 1 hour after the administration of physosigmine. In this respect, the patient's physical examination and vital signs should be followed closely by the clinician. It should be kept in mind that there may be excessive cholinergic activity in patients administered physostigmine, and the patient should be followed in this regard. The patient's cholinergic and anticholinergic signs and symptoms should be kept in balance. Diagnosis is very difficult in patients with poisoning, therefore, it has been reported that physostigmine is used for diagnostic purposes in some cases. However, it is not recommended to use physostigmine for diagnostic purposes. Physostigmine is contraindicated in cases of asthma, drug hypersensitivity, gastrointestinal or bladder obstruction, cardiac conduction disturbances and concomitant sodium channel blocker poisoning. In addition to all these approaches, the patient's supportive treatment should not be forgotten. If present, hyperthermia should be controlled. As a result of shivering, heat is released in the muscles. The use of benzodiazapines again should be considered to control tremor in patients who tremble in order to prevent heat generation. The use of dantrolene sodium in patients without muscle rigidity is not recommended. Again, benzodiazepines are recommended for the control of seizures due to anticholinergic toxidrome. Lorazepam or midazolam is recommended. Phenytoin has no place in the control of seizures. Most of the patients benefit greatly from medical therapy. Determination of the prognosis is usually

determined in the light of clinical signs and findings as a result of 6-8 hours of observation. Moderate and severe symptomatic patients were considered appropriate to be followed up in the intensive care unit (9-10).

2.Cholınergıc Toxidrome

Cholinergic toxidrome, in general terms, presents with a clinical picture opposite to anticholinergic toxidrome. The main drugs and active substances that cause cholinergic toxidroma are listed in Table 3. Acetylcholine takes part in the central nervous system, autonomic ganglia, postganglionic, parasympathetic nervous system and skeletal muscle motor junction. It performs its job by binding to muscarinic and nicotinic receptors. Acetylcholinesterase regulates acetylcholine activity in the synaptic cleft. Some factors that cause cholinergic toxidrome show their effects by inhibiting the acetylcholinesterase enzyme. As a result of the inhibition, acetylcholine accumulates in the synaptic cleft and leads to an excessive stimulation. Organophosphates, carbamate insecticides, tabun, sarin and VX gas come first among the active ingredients that cause cholinergic toxidroma. Since acetylcholine is found on almost the entire nervous system, it affects almost all organs and systems in cholinergic toxidroma. Its effects on the respiratory system are one of the main determinants of mortality. Acetylcholine causes more parasympathetic stimulation, therefore the clinical signs and symptoms of the patient are parallel to this. The patient has a marked increase in salivation. Secondary to bronchoconstriction, expiration is prolonged and wheezing occurs. Due to its effects on the circulatory system, the patient develops hypotension and bradycardia. This situation can lead to peripheral circulatory disorders. Due to its effects on the sweat glands, an increase in sweating occurs. Gastrointestinal effects include increased peristalsis and loss of sphincter tones. Nausea and vomiting may accompany. Colic pain, tenesmus and incontinence are seen. The increase in acetylcholine in the central nervous system causes the patient to have seizures. Fasciculations may occur due to stimuli in the motor

endplate. However, when its effect increases, it may result in flaccid paralysis. The symptoms to be observed for the follow-up of the symptoms and signs of the patients who have been poisoned due to cholinergic effective drugs or agents are briefly indicated in Table 4 (11-12).

Table 3. Drugs and active substances that cause cholinergic toxicrome

Acetylcholinesterase Inhibitors	**Direct Muscarinic Agonists**	**Nicotinic Agents**
Organic phosphate insecticides (malathion, parathion, diazinon)	Carbachol	Nicotine
Carbamate insecticides (aldicarb, carbaryl, propoxur)	Methacholin	Water hemlock
Chemical weapons (soman, sarin, tabun VX, cyclosarin)	Pilocarbine	
Medicines to reverse myasthenia gravis or neuromuscular drugs (physostigmine, pyridostigmine, neostigmine, edrophonium)	Muscarinic mushroom	

Table 4. Symptoms and signs in cholinergic poisoning

SYMPTOMS (SLUDGE)	**SYMPTOMS (DUMBELLS)**
Salivation	Defecation
Lacrimation	Urination
Urination	Miyosis
Defecation	Broncospasm
Gastrointestinal Pain	Broncore
Emesis	Lacrimation
	Salivation

For the diagnosis of cholinergic toxidroma; Suspicion of exposure to cholinergic agents, presence of clinical signs and symptoms, and support of special laboratory tests are sufficient. Plasma butyrylcholinesterase or pseudocholinesterase level measurements are helpful in diagnosis. However, these laboratory tests cannot be performed in every emergency room. Although routine laboratory tests are not specific for diagnosis, they can be guide. There is can be impraired in liver and kidney function tests. ECG changes can be seen in patients. The most common findings are ventricular arrhythmias, torsades depointes, idioventricular rhythm, atrioventricular blocks and prolongation of the QT interval (13).

Since cholinergic toxidrome has a very high mortality, its treatment should be started immediately. Airway patency should be achieved immediately. Supportive therapy for respiration and circulation should be continued. Exposure to agents or drugs that cause cholinergic toxidrome should be cutted immediately. If there is skin contact, clothing should be removed and the exposed area should be washed with warm soapy water. If the patient has taken it orally and admitted within the first two hours, gastric lavage should be evaluated. Activated charcoal should be considered if complications such as vomiting and aspiration are absent and airway patency can be achieved. Seizures due to cholinergic discharge should be kept under control. Benzodiazepines are recommended to keep seizures under control. Atropine is a competitive antagonist with acetylcholine on muscarinic receptors. It is the main antidote used in cholinergic toxidroma. The half-life of atropine in the human body is 2-5 hours. It eliminates the cholinergic effect on the respiratory, circulatory and gastrointestinal system. It helps in preventing hypersalivation. But; It is ineffective on muscle weakness and paralysis. In cholinergic toxidroma, atropine is initially recommended as 1-2 mg IV in mild to moderate poisoning and 3-5 mg IV in severe poisoning. It is recommended to be applied every 5 minutes in intervals. After reaching the sufficient dose and reaching the

target, the appropriate dose of infusion should be opened. The clinician should understand by following the clinical signs and symptoms that atropine has reached the appropriate dose. Atropinization targets are specified in table 5. Oximes act as reactivators of acetylcholinesterase enzyme. Organophosphates are bound to the enzyme acetylcholinesterase by irreversible and covalent bonds. This is called aging. Therefore, oximes should be given before aging occurs in organophosphate poisoning. It is generally recommended to be given within 24-48 hours. The effectiveness of oximes in vitro has been proven. However; In controlled studies in humans, no significant difference was found between the use of oximes in combination with atropine and the use of atropine alone. A slow bolus of 30 mg/kg IV followed by an IV infusion of 8 mg/kg/hour is recommended in adult and pediatric patients. The maximum dose for adults is 12 grams daily (14-16).

Table 5. Targets in atropine treatment

No wheezing of the lungs on auscultation
Heart rate >80 beats/minute
Pupillary return to normal
Dry underarm
Systolic blood pressure >80 mmHg

3.Sympatomymetıc Toxidrome

Sympathomimetic syndrome usually occurs as a result of abuse of substances such as cocaine, amphetamine, ephedrine. Drugs and agents that may cause sympathomimetic toxidroma are summarized in Table 6. In sympathomimetic toxidroma, the adrenergic system is activated. Excitations occur on the respiratory system, cardiovascular system, central nervous system, skin, eyes, and exocrine glands. As a result of the stimulation of the central nervous system, the patient experiences agitation, anxiety, tremor, delusions, and paranoia. The patient may have seizures. As a result of the excitation on the central system, the patient is in superhuman strength. For this reason, it is

very difficult and arduous to control the agitated patient. As a result of its effects on the cardiovascular system, tachycardia and hypertension are observed. Hypertensive crisis, aortic dissection, cardiac arrhythmias may develop. Effects on the eye are on mydriasis, visual disturbances. On the other hand, patients have hyperproxia and sweating (17-18).

Table 6. Drugs And Agents Wıth Sympatomymetıc Effect

Albuterol
Amphetamine and its derivatives (MDA, ecstasy)
Caffeine, nicotine
catecholamines
Cocaine
some decongestants (ephedrine, pseudoephedrine)
theophylline, aminophylline
Ketamine, phencyclidine, LSD
Phenyl propylamine
Some weight loss drugs

In sympathomimetic toxidroma, clinical findings are at the forefront. This helps in making the diagnosis. However, urine toxicological studies can still be done to support the diagnosis. Routine laboratory tests help detect additional pathologies. The patient's ECG should be evaluated, as ECG changes are expected. It should be noted that myocardial infarction may underlie chest pain in patients using sympathomimetic drugs. The approach to sympathomimetic toxidroma usually includes supportive care. There is no specific antidote application. The development of complications should be prevented. If complications develop, they should be brought under control. Airway patency can be achieved in patients poisoned by sympathomimetic drugs or agents, and gastric lavage should be evaluated in early admissions if agents are taken orally. Benzodiazepines are effective as a treatment option in patients with seizures or severe agitation. In addition, benzodiazepines contribute to controlling hypertension in agitated patients. Vasodilator drugs

such as hydralazine or nitroprusside can be used in patients who cannot be controlled with benzodiazepines. Hyperthermia should be controlled in the patient. Nitroglycerin and morphine may be preferred for angina pectoris. In addition, these drugs make it easier to control hypertension (19-22).

4.Opioid Toxidrome

While the definition of opioid includes only opium-derived narcotics, the definition of opioid includes all drugs and active substances that bind to opioid receptors. Opioids are responsible for opioid toxidroma. They form the clinic of the poisoned patient by binding to opioid receptors in various organs and systems of the body. They cause sedation and even coma by affecting the central nervous system. The patient remains hypoxic due to the suppression of breathing. Pupillary miotic clinical feature. This condition is called pinpoint pupil. The gastrointestinal tract is affected and intestinal peristalsis is reduced. Depending on the effect of different opioids, there may be differences in the clinic of opioid toxidroma according to the factors. Seizures, ECG changes, chest wall rigidity may be seen. The clinical findings of the patient may vary according to the duration and amount of exposure. However, in opioid toxidroma, bilateral miosis (pinpoint pupil), respiratory system depression, and central nervous system depression are seen briefly. Urine screening tests can be done to confirm the diagnosis. While natural opioids can be detected in the urine, synthetic opioids may not (23-24)

The first thing to do in patients with opioid toxidroma is to ensure airway patency. Monitoring is essential. Vital values should be tried to be kept stable. Fluid and oxygen support should be provided. Naloxane and naltrexone, which are used as antidotes in comatose patients, should be considered. Naloxane can be administered as an IV slow push at doses of 0.4-2 mg. Administration dose; It is titrated according to the amount of opioid taken, its formulation, the weight of the patient and whether it is opioid dependent. In patients whose vascular

access cannot be established, 2 mg of naloxane can be mixed with 3 ml of saline and applied to the nebulizer. The half-life of naloxane is approximately 1 hour. It can be given in repeated doses. It may produce naloxone withdrawal syndrome in opioid dependent patients. Symptoms such as vomiting, diarrhea, agitation, piloerection, sweating may occur (25-28).

5.Sedative Hypnotic Toxidrome

It is generally associated with depression of autonomic activity. It can cause a wide range of central depression from depression and sleepiness to coma and respiratory depression. As seen in opioid toxidrome, coma, hypotension, respiratory depression, miosis, hypothermia, hyporeflexia and decreased bowel sounds are seen. It occurs with drugs and factors that depress the central nervous system that do not bind to opioid receptors. These include benzodiazepines, valproate, and ethanol. Substances that cause sedative hypnotic toxidroma are summarized in Table 7. Agitation may be seen in patients with benzodiazepine-induced toxidroma, although they have central nervous system depression (29-31)

Table 7. Factors Causing Sedative Toxidroma

Benzodiazepine
Imidazopyridine (zolpidem, zopiclone)
barbiturates
meprobamate
sedative phenothiazine
phenytoin
sodium valproate
Ethanol high dose

It is necessary to urgently evaluate the patient, to ensure the patency of the airway and monitorized follow-up. Vital values should be kept stable. The concomitant use of the opioid antagonist naloxane and the benzodiazepine antagonist flumazenil should be considered in multiple drug intake.

Toxicological screening tests can help with multiple drug intake. However, there is no significant association of routine laboratory tests. The use of flumazenil in patients with ECG changes and seizures is not recommended. Flumazenil should be given initially at 0.2-0.3 mg IV followed by 0.1 mg per minute until clinical response. However, the total dose should not exceed 1-2 mg. If clinical response is not achieved when these doses are reached, alternative diagnoses should be re-evaluated (32-34)

6.Serotonin Toxidrome

The main cause of serotonin syndrome is the increase in the level of serotonin hormone in the synaptic gap. Serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), cyclic antidepressants and atypical antipsychotics can cause this condition. Drugs and factors that may cause serotonin toxidrome are summarized in Table 8. The use of these drugs and the evaluation of the patient's clinical condition signal to the clinician that serotonin syndrome has developed. Cognitive agitation, confusion, and hallucinations may occur. Myoclonus, tremor, pyramidal syndrome, seizure and even coma can be seen. Mydriasis and sweating may accompany. Hypertension, tachycardia, increased respiratory rate, hyperthermia, shivering are the classic findings. In routine laboratory tests, hyperglycemia, electrolyte disorders, and lactic acidosis can be detected. There is an increase in rigidity, hyperreflexia and foot clonus in the lower extremities. It can be confused clinically with anticholinergic toxidroma. In this case, the lower extremity tone, bowel sounds and dryness of the skin should be checked. Because decreased bowel sounds and dry skin are typically seen in anticholinergic syndrome, whereas in serotonin syndrome this is the opposite. These differences should alert the clinician. Clinic; occurs within a few hours of ingestion of the responsible drug. It can also occur a few weeks after taking some neuroleptic drugs (35-37)

One of the first things to be done in patients with serotonin syndrome is to discontinue the causative drug. Hyperthermia should be controlled and fluid support should be provided to the patient. Dantrolene and bromocriptine can be used to stabilize the patient. Benzodiazepines are recommended for the control of seizures in patients who develop seizures. It also plays an important role in the sedation of patients agitated with benzodiazepines. Cyproheptadine can be used as an antagonist in serotonin syndrome. Initially, 4-12 mg is used orally. In the patient who does not respond, the dose is repeated 2 hours later. If there is no clinical response from the patient given a total of 32 mg of cyproheptadine, the treatment is stopped. Since cyproheptadine is administered only orally, its efficacy is limited (38-40).

Table 8. Drugs That May Cause Serotonin Syndrome

MAO inhibitors
SSRI: Paroxetine, Sertraline, Citalopram, Escitalopram, Fluoxetine, Fluvoxamine
Trazodone, Mirtazapine, Venlafaxine
Analgesics: Tramadol, Meperidine
Amphetamine derivatives, LSD, Cocaine
Lithium
Tricyclic antidepressants
bupropion

7. Neuroleptic Malign Syndrome

It is a clinical condition that occurs due to the deficiency or insufficiency of dopamine in the central nervous system. Ingestion of Parkinson's medications or the use of dopamine antagonists can also cause this condition. Drugs that may be associated with neuroleptic malignant syndrome are listed in Table 9. Hyperthermia, rigidity, mental status disorder, autonomic instability are seen in patients. An increase in leukocytes and creatine phosphokinase can be detected in routine laboratory tests. In the first stage of treatment, the patient's vital values should be kept stable. Fluid support should be provided.

Electrolyte imbalance should be eliminated. Hyperthermia is unresponsive to antipyretics. Cold application can be made. The use of bromocriptine, dantrolene, and amantadine should be considered. However, although it is recommended, its effectiveness has not been clearly proven. The use of benzodiazepines should be considered in patients with seizures (41-45).

Table 9. Drugs That May Cause Neuroleptic Malignant Syndrome

Typical Neuroleptics (haloperidol, chlorpromazine, fluphenazine, thioridazine, triflordazine, thioticene, loxapine, bromperidol, promazine, clopenthixol)
Atypical Neuroleptics (olanzapine, clozapine, risperidone, quetiapine, ziprasidone, aripiprazole, zotepine, amisulpiride)
Antiemetics (droperidol, domperidone, metoclopramide, promethazine, prochlormethazine)
Dopaminergic Agent Withdrawal (levodopa, amantadine, tolcapone, dopamine agonists)
Tetrabenazine, Reserpine, Amoxapine, Diatrizoate, Lithium, Phenelzine, Dosulepin, Trimipramine, Desipramine

REFERENCES

1. Ciottone G. R. (2018). Toxidrome Recognition in Chemical-Weapons Attacks. The New England journal of medicine, 378(17), 1611–1620. https://doi.org/10.1056/NEJMra1705224
2. Rasimas, J. J., & Sinclair, C. M. (2017). Assessment and Management of Toxidromes in the Critical Care Unit. Critical care clinics, 33(3), 521–541. https://doi.org/10.1016/j.ccc.2017.03.002
3. Holstege, C. P., & Borek, H. A. (2012). Toxidromes. Critical care clinics, 28(4), 479–498. https://doi.org/10.1016/j.ccc.2012.07.008
4. Hernandez, S. H., & Nelson, L. S. (2010). Prescription drug abuse: insight into the epidemic. Clinical pharmacology and therapeutics, 88(3), 307–317. https://doi.org/10.1038/clpt.2010.154
5. Rodrigues, M. C., & Oliveira, C. d. (2016). Drug-drug interactions and adverse drug reactions in polypharmacy among older adults: an integrative review. Revista latino-americana de enfermagem, 24, e2800. https://doi.org/10.1590/1518-8345.1316.2800
6. Broderick, E. D., Metheny, H., & Crosby, B. (2022). Anticholinergic Toxicity. In StatPearls. StatPearls Publishing.
7. Ghossein, N., Kang, M., & Lakhkar, A. D. (2022). Anticholinergic Medications. In StatPearls. StatPearls Publishing.
8. Huynh, D. A., Abbas, M., & Dabaja, A. (2022). Diphenhydramine Toxicity. In StatPearls. StatPearls Publishing.
9. Dawson, A. H., & Buckley, N. A. (2016). Pharmacological management of anticholinergic delirium - theory, evidence and practice. British journal of clinical pharmacology, 81(3), 516–524. https://doi.org/10.1111/bcp.12839
10. Saadi, R., & Bohnenberger, K. (2020). Physostigmine for Antimuscarinic Toxicity. Journal of emergency nursing, 46(1), 126–128. https://doi.org/10.1016/j.jen.2019.09.002
11. Pakala, R. S., Brown, K. N., & Preuss, C. V. (2022). Cholinergic Medications. In StatPearls. StatPearls Publishing.

12. Weinbroum A. A. (2005). Pathophysiological and clinical aspects of combat anticholinesterase poisoning. British medical bulletin, 72, 119–133. https://doi.org/10.1093/bmb/ldh038
13. King, A. M., & Aaron, C. K. (2015). Organophosphate and carbamate poisoning. Emergency medicine clinics of North America, 33(1), 133–151. https://doi.org/10.1016/j.emc.2014.09.010
14. Raszewski, G., & Filip, R. (2004). Oksymy w leczeniu zatruć zwiazkami fosforoorganicznymi [Use of oximes in the therapy of acute intoxication by organophosphorus compounds]. Przeglad lekarski, 61(3), 181–184.
15. Cannard K. (2006). The acute treatment of nerve agent exposure. Journal of the neurological sciences, 249(1), 86–94. https://doi.org/10.1016/j.jns.2006.06.008
16. Eddleston, M., Buckley, N. A., Eyer, P., & Dawson, A. H. (2008). Management of acute organophosphorus pesticide poisoning. Lancet (London, England), 371(9612), 597–607. https://doi.org/10.1016/S0140-6736(07)61202-1
17. Brown, H., & Pollard, K. A. (2021). Drugs of Abuse: Sympathomimetics. Critical care clinics, 37(3), 487–499. https://doi.org/10.1016/j.ccc.2021.03.002
18. King, A., Dimovska, M., & Bisoski, L. (2018). Sympathomimetic Toxidromes and Other Pharmacological Causes of Acute Hypertension. Current hypertension reports, 20(1), 8. https://doi.org/10.1007/s11906-018-0807-9
19. 19. Avşaroğulları, L. (2020). Emergency Approaches Before Intensive Care in Poisoning . Aksaray University Journal of Medical Sciences, 1st National Multicentric Multidisciplinary Toxicology Symposium, 37-43. Retrieved from https://dergipark.org.tr/en/pub/asujms/issue/55099/825022
20. Gray SD, Fatovich DM, McCoubrie DL et al. Amphetamine related presentations to an inner city tertiary emergency department: a prospective evaluation. Medical Journal of Australia 2007; 186(7):336-339.
21. Hatsukami DK, Fischman MW. Crack cocaine and cocaine hydrochloride. Are the differences myth or reality? Journal of the American Medical Association 1996; 276:1580-1588.

22. Kiszka M. (2003). Toksyczność kokainy [Cocaine toxicity]. Archiwum medycyny sadowej i kryminologii, 53(2), 151–166.
23. Sachdeva, D. K., & Stadnyk, J. M. (2005). Are one or two dangerous? Opioid exposure in toddlers. The Journal of emergency medicine, 29(1), 77–84. https://doi.org/10.1016/j.jemermed.2004.12.015
24. Häkkinen, M., Launiainen, T., Vuori, E., & Ojanperä, I. (2012). Comparison of fatal poisonings by prescription opioids. Forensic science international, 222(1-3), 327–331. https://doi.org/10.1016/j.forsciint.2012.07.011
25. Dolinak D. (2017). Opioid Toxicity. Academic forensic pathology, 7(1), 19–35. https://doi.org/10.23907/2017.003
26. Baldo B. A. (2021). Toxicities of opioid analgesics: respiratory depression, histamine release, hemodynamic changes, hypersensitivity, serotonin toxicity. Archives of toxicology, 95(8), 2627–2642. https://doi.org/10.1007/s00204-021-03068-2
27. Prekupec, M. P., Mansky, P. A., & Baumann, M. H. (2017). Misuse of Novel Synthetic Opioids: A Deadly New Trend. Journal of addiction medicine, 11(4), 256–265. https://doi.org/10.1097/ADM.0000000000000324
28. Dezfulian, C., Orkin, A. M., Maron, B. A., Elmer, J., Girotra, S., Gladwin, M. T., Merchant, R. M., Panchal, A. R., Perman, S. M., Starks, M. A., van Diepen, S., Lavonas, E. J., & American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research; and Council on Clinical Cardiology (2021). Opioid-Associated Out-of-Hospital Cardiac Arrest: Distinctive Clinical Features and Implications for Health Care and Public Responses: A Scientific Statement From the American Heart Association. Circulation, 143(16), e836–e870. https://doi.org/10.1161/CIR.0000000000000958
29. Allen, L., & Alsalim, W. (2006). Best evidence topic report. Gammahydroxybutyrate overdose and physostigmine. Emergency medicine journal : EMJ, 23(4), 300–301. https://doi.org/10.1136/emj.2006.035139

30. Roberts, D. M., & Buckley, N. A. (2011). Enhanced elimination in acute barbiturate poisoning - a systematic review. Clinical toxicology (Philadelphia, Pa.), 49(1), 2–12. https://doi.org/10.3109/15563650.2010.550582
31. Kang, M., Galuska, M. A., & Ghassemzadeh, S. (2022). Benzodiazepine Toxicity. In StatPearls. StatPearls Publishing.
32. Nordt, S. P., & Clark, R. F. (1997). Midazolam: a review of therapeutic uses and toxicity. The Journal of emergency medicine, 15(3), 357–365. https://doi.org/10.1016/s0736-4679(97)00022-x
33. Lader, M., & Petursson, H. (1983). Rational use of anxiolytic/sedative drugs. Drugs, 25(5), 514–528. https://doi.org/10.2165/00003495-198325050-00004
34. Iorga, A., & Horowitz, B. Z. (2022). Phenytoin Toxicity. In StatPearls. StatPearls Publishing.
35. Talton C. W. (2020). Serotonin Syndrome/Serotonin Toxicity. Federal practitioner : for the health care professionals of the VA, DoD, and PHS, 37(10), 452–459. https://doi.org/10.12788/fp.0042
36. Bartlett D. (2017). Drug-Induced Serotonin Syndrome. Critical care nurse, 37(1), 49–54. https://doi.org/10.4037/ccn2017169
37. Boyer, E. W., & Shannon, M. (2005). The serotonin syndrome. The New England journal of medicine, 352(11), 1112–1120. https://doi.org/10.1056/NEJMra041867
38. Wang, R. Z., Vashistha, V., Kaur, S., & Houchens, N. W. (2016). Serotonin syndrome: Preventing, recognizing, and treating it. Cleveland Clinic journal of medicine, 83(11), 810–817. https://doi.org/10.3949/ccjm.83a.15129
39. Simon, L. V., & Keenaghan, M. (2022). Serotonin Syndrome. In StatPearls. StatPearls Publishing.
40. Maitland, S., & Baker, M. (2022). Serotonin syndrome. Drug and therapeutics bulletin, 60(6), 88–91. https://doi.org/10.1136/dtb.2021.000032
41. Perry, P. J., & Wilborn, C. A. (2012). Serotonin syndrome vs neuroleptic malignant syndrome: a contrast of causes, diagnoses, and management. Annals of clinical psychiatry : official journal

of the American Academy of Clinical Psychiatrists, 24(2), 155–162.
42. Simon, L. V., Hashmi, M. F., & Callahan, A. L. (2022). Neuroleptic Malignant Syndrome. In StatPearls. StatPearls Publishing.
43. Pileggi, D. J., & Cook, A. M. (2016). Neuroleptic Malignant Syndrome. The Annals of pharmacotherapy, 50(11), 973–981. https://doi.org/10.1177/1060028016657553
44. Ware, M. R., Feller, D. B., & Hall, K. L. (2018). Neuroleptic Malignant Syndrome: Diagnosis and Management. The primary care companion for CNS disorders, 20(1), 17r02185. https://doi.org/10.4088/PCC.17r02185
45. Tormoehlen, L. M., & Rusyniak, D. E. (2018). Neuroleptic malignant syndrome and serotonin syndrome. Handbook of clinical neurology, 157, 663–675. https://doi.org/10.1016/B978-0-444-64074-1.00039-2

CHAPTER 28

GERIATRIC PATIENTS AND POLYPHARMACY

Assist. Prof. Dr. Şeyda Tuba SAVRUN[1],
Assist. Prof. Dr. Atakan SAVRUN[2],
Emergency Medicine Physician Rahime Şahin TURAN[3],
Research Assistant Furkan ELMAS[4],
Research Assistant İshak ÖZKAY[5]

[1] Ordu University, Faculty of Medicine, Emergency Department, Ordu, Turkey
dr.seyda.tuba@gmail.com, Orcid ID: 0000-0002-6512-2987
[2] Ordu University, Faculty of Medicine, Emergency Department, Ordu, Turkey
atakan4601@hotmail.com, Orcid ID: 0000-0001-7468-4159
[3] Ordu University Training and Research Hospital, Emergency Service, Ordu, Turkey,
drrahime28@hotmail.com, Orcid ID: 0000000280672944
[4] Ordu University, Faculty of Medicine, Emergency Department, Ordu, Turkey
dr.felmas@gmail.com, Orcid ID: 0000-0002-3806-6246
[5] Ordu University, Faculty of Medicine, Emergency Department, Ordu, Turkey
ishakozkay@gmail.com, Orcid ID: 0000-0002-1183-4188

İntroduction

The advancement of technology has brought positive developments in the field of health. This has contributed to the prolongation of people's life spans. The World Health Organization (WHO) estimates that while 12% of the population was 60 years and older in 2015, this rate will increase to 22% in 2050 (1). Looking at the United States (USA) data; It has been reported that while the population over the age of 65 was approximately 35 million in 2001, this number is estimated to increase to 70 million in 2030 (2). Considering the population aged 65 and over in Turkey; It has been reported that there are 7 million 953 thousand 555 people in 2020 and the ratio of this group to the total population is 9.5%. In addition, it is estimated that the ratio of this group to the total population will increase by 11.0% in 2025, 12.9% in 2030, 16.3% in 2040, 22.6% in 2060 and 25.6% in 2080 (3).

Due to aging, there are some physiopathological changes in our body. In many organs and systems, functional reserves may decrease. Due to aging, many physiopathological conditions that negatively affect the person may occur, such as decrease in sensory abilities such as vision and hearing, regression in physical and mental levels, decrease in balance potential, decrease in adaptation to changing environmental conditions, weakening of the immune system, delay in wound healing. This situation causes the emergence of comorbid diseases, especially in the elderly, or the symptomaticization of existing but asymptomatic diseases (4). In addition, pictures that manifest themselves with atypical symptoms but cannot be classified into a complete disease group can also be seen in elderly people. In other words, clinical pictures that are frequently encountered in elderly patients, which can impair quality of life and increase morbidity and mortality, may be encountered. This condition is called geriatric syndromes (5,6,7,8)

Polypharmacy is the simultaneous use of more than one drug for different reasons. There are different definitions for polypharmacy in the literature (9,10,11,12).

- Use of 2 or more drugs for at least 240 days
- The use of 2 or more drugs without specifying the time
- The use of at least 4 drugs in the National Service Framework (NSF)
- Use of 5 or more drugs

It has been reported that the physiopathological changes that occur due to aging both cause the use of multiple drugs due to symptoms, and increase the risk of drug side effects and interaction between drugs by affecting the pharmacodynamics and pharmacokinetics of drugs (13)

Epidemiology

People of all age groups use drugs for different indications. However, when we look at the population, it has been reported that the group that uses the most drugs according to the population ratio is the elderly people. In a study conducted in the USA, it was reported that although people over the age of 65 in the country constitute 13% of the total population, 30% of all prescriptions were written for this group (14). In a similar study conducted in England, although people over the age of 60 constitute 20% of the total population, approximately 52% of the prescriptions written by doctors were written only for this group, and even 36% of individuals over the age of 75 combined 4 or more drugs. It has been reported that women over 65 use 5 or more drugs, and 12% use 10 or more drugs(15). Another study in the literature reported that 57-59% of people over the age of 65 use 5 or more drugs per week, and 17-19% use 10 or more drugs per week (16). In a study conducted in Turkey, 84.7% of the elderly people aged 65 and over stated that they used at least one drug continuously, and 38.2% of them used four or more drugs (17). According to a review in the literature, it was reported that polypharmacy was expressed as ≥5 drugs and the rate of polypharmacy ranged from 38.1% to 91.2%. In the same study, it was reported that the prevalence of those using ≥ 9 drugs was 12.8–74.4%, while the prevalence of those using ≥ 10 drugs was between 10.6–65.0%(18).

Etiology

There are many reasons for the use of multiple drugs in elderly patients. Among them; presence of comorbidity, malnutrition, immobilization, incontinence, depression, delirium, dementia, falling, gait disturbances, pain, pressure sores, instability, loss of intellectual function, infection, impaired vision and hearing, iatrogenic diseases, insomnia, immunodeficiency, living in a nursing home, patient and caregiver-related factors. In addition, the physician's lack of education about the disease, drug prescribing, drug side

effects, and drug-drug interaction can be counted (8). As mentioned above, there may be many reasons for the use of multiple drugs, but the presence of multiple comorbidities among them is a very important etiological factor. In a study conducted in Turkey, it was reported that 90% of individuals over the age of 65 had one chronic disease, 35% had two, 23% had three, and 14% had four or more chronic diseases(19). Even in the treatment guidelines, the use of multiple drugs may be recommended to treat the chronic disease. In this respect, it has been reported that at least 5 drugs can be used in people with more than one comorbid disease (20).

It has been reported that the incidence of drug-drug interactions increases in the elderly who use more than one drug, and that the drug-drug interaction, mediated by the potential hepatic cytochrome enzyme, can reach a high value of 80% in the elderly who use 5 or more drugs. In fact, it has been reported that the risk of interaction increases as the number of drugs used increases. It has been reported that while the probability of drug-drug interaction is approximately 50% in the elderly who use 5 to 9 drugs, this rate increases to 100% when 20 or more drugs are used (21). Similarly, treating the side effects of a drug used with another agent can also cause polypharmacy. Gastric protective drugs are mostly prescribed for this reason (22).

Another situation that causes polypharmacy is that patients start taking medication without a doctor's examination, such as at their own request or friend's recommendation. He knows that even because of the side effects of the drugs that are started, another drug can be applied and a vicious circle can be entered. In a study conducted in Turkey, it was reported that 21.1% of the population used drugs with their own decision, 13.2% with the recommendation of a friend, 7.9% with the advice of a pharmacist, and 5.2% with the recommendation of a neighbor (23). Similarly, in a study conducted abroad, it was reported that approximately 50% of elderly patients using 5 or more drugs used drugs without the supervision of a doctor (24).

Results of Polypharmacy

As in all age groups, the main purpose of drug use in the geriatric patient group is for the patient's recovery and elimination of symptoms. However, this table may change in the case of polypharmacy. The frequency of drug side effects, drug-drug interactions, treatment incompatibility due to multiple drug

use, cost expenditures, and hospitalizations increase in patients (25). Physiopathological changes that occur with age in geriatric patients affect all organs. This situation causes changes in the pharmacodynamics and pharmacokinetics of the drugs taken. Especially the accompanying comorbid diseases negatively affect the side effects and interaction of drugs with each other. For this reason, the effect and side effects of the drug used in young adult patients are not always the same in geriatric patients. For this reason, it may cause changes in the dose of drug use in patients or further progression of polypharmacy. In the literature, it has been reported that polypharmacy-related weight loss, frequency of falls, hip fracture, metabolic and mental dysfunction are adversely increased (26-28). In the literature, it has been reported that while the risk of side effects is 6% in geriatric cases using two drugs, this rate approaches 100% in the use of 8 or more drugs (29).

Many different methods and guidelines have been proposed to prevent the negative effects of polypharmacy on the health of elderly patients due to drug-drug interactions and adverse drug reactions. Among these are the following:

- Drug Burden Index
- Age assessment tool
- Beers Criteria
- START (Screening Tool to Alert doctors to Right Treatment) and STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions)

Drug Burden Index (A Drug Burden Index) is a model that includes anticholinergic and sedative effects, inappropriate drugs, total number of drugs and daily doses. In order to evaluate whether drug therapy is suitable for the elderly patient, it is the calculation of individual physiological age based on chronological age and self-reported health status.

Beer's criteria is one of the guidelines created to prevent the negative effects of polypharmacy. Beer's criteria were considered insufficient. For this reason, a new guideline called STOPP/START (Screening Tool of Older Person's potentially inappropriate Prescriptions/Screening Tool to Alert doctors to the Right, i.e. appropriate, indicated Treatment) has been developed.

STOPP/START guide is a guide designed to create a comprehensive, evidence-based list. In addition, consensus was aimed in the fields of geriatric

medicine, aging psychiatry and pharmacy. In this way, it is aimed to determine drug interactions and to detect drugs that are not prescribed when indicated. However, the effectiveness of the guidelines is limited, sufficient number and level of evidence could not be provided. However, drugs and drug groups reported by these criteria should not be prescribed to elderly patients (30).

Conclusion

To reduce polypharmacy and possible complications; It is very important as a first step to learn the generic names of all medicines, whether prescription, over-the-counter or herbal medicine, from which group and for which indication they are used. It is necessary to know the side effects, drug interactions, and age-related pharmacology of the drugs used. Side effects of drugs should be followed closely. If a new drug is to be started, it should be started at a low dose. When discontinuing drugs, they should be discontinued as slowly as possible. However, the most important point is to treat with as few drugs as possible and to avoid polypharmacy.

References

1. World Health Organization. Ageing and Health, 2022. Erişim Linki: https://www.who.int/news-room/fact-sheets/detail/ageing-and-health [Access Date: 17.10.2022]
2. Fulton MM, Allen ER. Polypharmacy in the elderly: a literatüre review. J Am Acad Nurse Pract. 2005;17:123-132
3. Turkish Statistical Institute. Seniors with Statistics, 2022. Access Link: https://www.tuik.gov.tr/Home/Index [Access Date:31.10.2022]
4. Oktem B, Uzer F. General Characterıstıcs of The Geriatric Patıent Population in The Emergency Department. Kocatepe Medical Journal,2022;23(3):283-87
5. Cigolle CT, Langa KM, Kabeto MU, et al. Geriatric Conditions and Disability: The Health and Retirement Study. Ann Intern Med 2007; 147(3):156-164.
6. Anpalahan M, Gibson SJ. Geriatric Syndromes as Predictors of Adverse Outcomes of Hospitalization Internal Medicine Journal 2008; 38:16–23.
7. Sleeper RB. Common Geriatric Syndromes and Special Problems.The Consultant Pharmacists 2009; 24:6447-6462.
8. Kane L, Ouslander JG, Abrass IB, Resnick B eds. The Geriatric patient: Demography, epidemiology, and health services utiliza tion. In: Essentials of Clinical Geriatrics. 6th ed. Mc Graw Hill, USA, 2009:19-21
9. Veehof L, Stewart R, Haaijer-Ruskamp F, et al. The development of polypharmacy. A longitudinal study. Fam Pract. 2000; 17: 261-267.
10. Bjerrum L, Sogaard J, Hallas J, et al. Polypharmacy: correlations with sex, age and drug regimen. A prescription database study.Eur J Clin Pharmacol. 1998; 54: 197-202.

11. Medicines and older people: implementing medicines-related aspects of the NSF for older people. http://www.gov.uk/nsf/olderpeople/htm
12. Linjakumpu T, Hartikainen S, Klaukka T, et al. Use of medications and polypharmacy are increasing among the elderly. J Clin Epidemiol. 2002; 55: 809-817.
13. Hanlon JT, Linblad CI, Hajjar ER, et al. Update on drug-related problems in the elderly. Am J Geriatr Pharmacother. 2003;1:38-43.
14. Kaufman DW, Kelly JP, Rosenberg L, et al. Recent patterns of medication use in the ambulatory adult population of the UnitedStates: the Slone survey. JAMA. 2002; 287: 337–344.
15. Lesage J. Polypharmacy in the geriatric patient. Nurs Clin North Am 1991; 26: 273–290.
16. Cankurtaran M, Yavuz BB, Halil M, et al. Polypharmacy in elderly:Does evidence based medicine brings more drug useage? 3rd European Geriatrics congress. The journal of Nutrition, Health, Aging. 2004; 8: 280
17. Gökçe Holy Y. Multiple drug use in the elderly (Polypharmacy inelderly). Turk J Geriatric 2006; Special Issue: 37-44.
18. Jokanovic, N., Tan, E. C., Dooley, M. J., Kirkpatrick, C. M., & Bell, J. S. (2015). Prevalence and factors associated with polypharmacy in long-term care facilities: a systematic review. Journal of the American Medical Directors Association, 16(6), 535-e1.
19. Prak I, Soydal T, Bal E et al. Elderly Health. T.R. Ministry of Health, General Directorate of Basic Health Services. Pelin Ofset, Ankara. 2002; 67-71.
20. Drug prescribing for older adults [article online], 2014. Section Editor: Schmader KE, Deputy Editor: Sokol HN. Available from http://www.uptodate.com/contents/drug-prescribingfor-olderadults?

topicKey=PC%2F3013&elapsedTimeMs=4&view=print&displayedView=full. Erişim 5 Ekim 2017.

21. Tanrıover O. Multiple Drug Use in the Elderly. Clinical Medicine Family Medicine 2017;(9).6.31-33
22. Rochon PA. Drug prescribing for older adults. Section Editor: Schmader KE, Deputy Editor: Sokol HN. UpToDate. Last updated June 2011.
23. Arslan Ş, Atalay A, Gökçe-Kutsal Y. Drug consumption in the elderly. Turkish Journal of Geriatrics. 2000; 3: 56-60.
24. Tsuji-Hayashi Y, Kurokawa S. American Geriatrics Society 1999; 47: 1425-1429.
25. Hanlon JT, Linblad CI, Hajjar ER, et al. Update on drug-related problems in the elderly. Am J Geriatr Pharmacother. 2003;1:38-43.
26. Geriatrics and Gerontology. Halil M; Polypharmacy in Elderly Patients. 1st Edition Ankara MN Medikal & Nobel. 2006: 393-400.
27. Chrischilles E, Rubenstein L, Van Gilder R, et al. Risk factors for adverse drug events in older adults with mobility limitations in the community setting. J Am Geriatr Soc. 2007; 55: 29–34.
28. Agostini JV, Han L, Tinetti ME. The relationship between number of medications and weight loss or impaired balance in older adults. J Am Geriatr Soc. 2004; 52: 1719–1723.
29. Zagaria MAE. Pharmaceutical care of the older patient. US Pharm. 2000; 25: 94-95.
30. Yeşil, Y., Cankurtaran, M., & Jewellery, M. E. (2012). Polypharmacy. Clinical Development, 25(3), 18-23.

CHAPTER 29

GENERAL APPROACH TO POISONED PATIENT

M.D. Adem KÖKSAL[1]
Res. Asst. Yusuf Burak KALAFAT[2]
Res. Asst. Furkan KARA[3]

[1] Ordu University Education and Research Hospital, Department of Emergengy Medicine, Ordu, Türkiye. ademkoksal61@gmail.com, Orcid ID:0000-0001-8451-7397
[2]Ordu University, Faculty of Medicine, Department of Emergengy Medicine, Ordu Türkiye. yburakk52@gmail.com, Orcid ID: 0000-0001-6268-4725
[3] Ordu University, Faculty of Medicine, Department of Emergengy Medicine, Ordu Türkiye.

INTRODUCTION

The phrase of Paracelsus that "it is the dose that separates the poison from the medicine" has been valid from the Middle Ages to the present day. Poisoning; it is defined as the temporary or permanent damage to the organism by mineral, vegetable, animal or synthetic substances that impair human health and cause damage or death when a certain amount enters the body (1,2).

Substances that are harmful to the human body are called toxic substances, while the effects of these substances are called toxic effects. The dose of the chemical reveals the difference between the drug and the poison, as Paraselcelsus said. The amount used to treat the pathological processes occurring in the person is called the treatment dose (3). The dose in which the toxic effects of drugs are seen is called the minimal toxic dose, and the dose that causes death is called the lethal dose (1).

Poisoning factors differ according to countries and living conditions. In societies with more agricultural activities, pesticides may be exposed more frequently, and in societies living in countries close to the equator belt, reptile-derived poisons may be exposed more frequently. Self-harm usually occurs with readily available agents and drugs. For example, in the UK, paracetamol (acetaminophen) is the most common suicidal poison (4).

According to the data of the American Poison Control Center (AAPCC); when the hospital admissions with poisoning in 2017 were examined, 18.92% of them were for suicide purposes and 77.03% of them were accidental, among the top five poisoning agents; drugs and corrosive substances and subgroups of these two groups (5).

Numerous classifications of poisonings have been made in the historical development (3). It is obvious that classification made from a single perspective cannot provide sufficient information for the definition of poisoning. Depending on the duration and frequency of exposure, it can be divided into three groups as acute, subacute and chronic (3). While it is classified as suicide, accidental and criminal poisonings according to the cause of occurrence (3), it is classified as gastrointestinal, respiratory, skin contact and parenteral poisonings according to the route of entry of the agent into the body (6–8).

Initial Evaluation

Basic Approach

In order to stabilize the patient, to prevent possible problems and to take the necessary emergency measures, all patients are taken to the security circle and a quick initial examination is made in a short time. After securing the airway, circulation, and respiration, as we do in critically ill patients presenting to the emergency department, vital signs, mental status, pupil size, and skin

temperature are evaluated. Emergency diagnostic studies to be performed include oxygen saturation, continuous cardiac monitoring, an electrocardiogram (ECG), and spot fingertip blood glucose measurement. In all severe cases, an intravenous (IV) line should be established. Cervical immobilization should be provided in patients with suspected trauma. Intubation should always be kept in mind in patients with suspected aspiration. It is necessary to intervene in accordance with the advanced cardiac life support guideline in patients brought in as cardiac arrest (9).

Diagnosis

The first thing that should be done to the patient in poisoning cases in the emergency department is supportive treatment (10). However, it is ideal to know what the poisoning agent is and to apply specific treatment if possible (10). Although diagnostic tools in toxicology start with whole body samples that can be obtained and continue with advanced imaging methods, it is seen that all these tests are not meaningful in practice (10). The symptoms of patients who apply to the Emergency Departments with the suspicion of poisoning vary, are usually not specific, and therefore, it may not be understood that the patient is a poisoning case at the first presentation (10). For this reason, toxicology screening tests such as history taken from the first admission, physical examination, biochemical tests, blood gas measurements, radiography, ECG (electrocardiography), RIA (radioimmunoassay) and spectrometer analyzes can be instructive (10). In particular, it should be noted that patients who do not present as intoxication can only be diagnosed with these measurements and methods (10).

Story

Although the patient's history is the most useful source of information in determining the etiology of poisoning, it is generally not reliable after suicidal ingestion (11, 12). In a prospective study, the initial history was fully correlated with confirmatory testing in only 31% of cases (13). Since the patient may deteriorate due to the effect of medication or a psychiatric illness, she may not be able to give a reliable history (14). The signs, symptoms, and laboratory data expected from poisoning with the agent or agents in the history may help confirm the patient's history. If the patient is unable or unwilling to give a reliable history of exposure to a toxic substance, information should be obtained from healthcare professionals, the police, and the patient's employer, family and friends, as well as medical records and past drug use (9). A thorough investigation of the intoxication setting should be done to find boxes of pills or a suicide note that may provide clues to the etiologic agent or agents. Unknown pills or chemicals can be identified by consulting a regional poison control

center, computerized drug or poison identification system, or product manufacturer (for example, material data safety sheet) (9). In particular, the use of over-the-counter agents, traditional or herbal medicines, and vitamin supplements should be questioned in the history. Because they are not generally accepted as drugs by patients.

Physical Examination

After initial diagnostic evaluation and stabilization, other physical findings should be investigated to further identify a particular toxidroma Table 1) and narrow down potential etiologies of poisoning. Remarkably, a given patient may not exhibit all the symptoms or signs typically associated with a particular toxicrome. As an example, tricyclic antidepressants, despite being anticholinergic, can cause miosis due to competing effects resulting from activation of muscarinic and alpha receptors. If a patient has a mixed overdose (eg, heroin and methamphetamine), the pupils will likely be moderate rather than miotic or dilated (9). In cases of poisoning, some findings of the patients may give clues about poisoning. Sharp odors, pupil sizes, mental status changes, movement disorders, respiratory abnormalities, cardiovascular system abnormalities and skin findings that can be detected in physical examination can help to find out which substance the poisoning is due to (9).

Table 1. Toxidromes and clinical results

Toxidrome	Mental status	Vital signs	Skin	Pupils	Other manifestations	Examples of causative agents
Excitatory						
Sympathomimetic	• Hipervigilance • Agitated delirium (can be violent) • Hallucinations • Paranoia	**T:** Increased **HR:** Increased **RR:** Increased **BP:** Increased	Wet	Dilated	• Seizures • Widened pulse pressure	• Amphetamines • Cocaine • Cathinones • Ephedrine • Phenylpropanolamine • Pseudoephedrine
Hallucinogenic	• Hallucinations • Perceptual distortions (typically visual) • Depersonalization • Synesthesia • Agitation (can sometimes occur and whitout delirium)	**T:** Increased or normal **HR:** Increased or normal **RR:** Increased or normal **BP:** Increased or normal	Variable	Dilated (usually)	• Nystagmus (phencyclidine, ketamine) • Tachycardia, hypertension, agitated delirium (designer phenethylamines)	• Designer phenethylamines and tryptamines (eg, MDMA ("ecstasy"), MDEA) • Ketamine and methoxetamine • LSD and psilocybin • Phencyclidine • Mescaline
Anticholinergic	• Hipervigilance • Agitated delirium (usually easily controlled) • Hallucinations (picking at objects in air) • Mumbling speech (described as 'mouth full of marbles')	**T:** Increased **HR:** Increased (but may be normal in early poisoning) **RR:** Increased **BP:** Increased or normal	Dry and flushed	Dilated	• Dry mucous membranes • Decreased bowel sounds • Urinary retention • Choreoathetosis • Seizures (rare)	• Diphenhydramine (and other antihistamines) • Atropine and similar agents (hyoscyamine, dicyclomine, scopolamine, and naturally occurring belladonna alkaloids (eg, jimson weeds)) • Tricyclic antidepressants • Cyclobenzaprine • Orphenadrine • Phenothiazines
Serotonin syndrome (serotonin toxicity)	• Agitated delirium • Confusion • Awake and unresponsive	**T:** Increased **HR:** Increased **RR:** Increased **BP:** Increased	Wet, flushed or normal	Dilated	• Tremor, hyperreflexia, clonus (typically in lower extremities • Roving eye movements (ocular clonus) • Diarrhea	• MAOIs • Tricyclic antidepressants • SSRIs and SNRIs • Dextromethorphan • Meperidine • Refer to UpToDate content on combinations of agents that can cause serotonin syndrome
Inhibitory						
Cholinergic	• Sedation • Confusion • Stupor • Coma	**T:** Normal **HR:** Low (may be increased in early poisoning **RR:** Decreased or increased **BP:** Decreased or normal	Wet	Constricted	• Seizures (typically occur early) • Salivation • Urinary and fecal incontinence • Vomiting, diarrhea, abdominal cramps • Bronchorrhea and bronchoconstriction • Muscle fasciculations and paralysis • Weakness	• Organophosphate and carbanate insecticides • Nerve agents (eg, VX, tabun, sarin, soman and Novichok) • Nicotine • Physostigmine • Rivastigmine • Bethanechol • Pilocarbine • Urecholine
Opioid	• Sedation • Coma	**T:** Decreased or normal **HR:** Decreased or normal **RR:** Decreased or apneic **BP:** Decreased or normal	Variable	Constricted (may be pinpoint)	• Noncardiogenic pulmonary edema • Needle marks • Can develop hypotension	• Opioids (eg, fentanyl and analogues, heroin, morphine, methadone, oxycodone, hydromorphone) • Diphenoxylate • Loperamide
Sedative-hypnotic	• Sedation • Confusion • Stupor • Coma	**T:** Decreased or normal **HR:** Decreased or normal **RR:** Decreased, apneic or normal **BP:** Decreased or normal	Variable	Variable	• Nystagmus • Barbiturates can cause respiratory depression or apnea • In most cases, isolated benzodiazepine ingestions do not cause respiratory depression • Cyclical coma and myoclonic encephalopathy (carisoprodol, meprobamate, glutethimide)	• Benzodiazepines • Barbiturates • Ethanol and other alcohols • Gabapentin and pregabalin • Zolpidem • Carisoprodol • Meprobamate • Glutethimide

Characteristic odors; Acetone odor in ethanol, isopropyl alcohol, chloroform, salicylate poisonings; bitter almond odor in cyanide poisoning; The smell of garlic in arsenic, phosphorus, thallium, selenium poisoning (9).

Pupillary manifestations: Mydriasis: Sympathomimetics (cocaine, caffeine, ephedrine, amphetamine), anticholinergics (atropine, scopolamine, antihistaminic, antiparkinsonian agents, phenothiazines), hallucinogens (LSD, mescaline, psilocybin), glutemid, MAOIs, syndrome, nico drug withdrawal

syndrome. Miosis: opioid (heroin, morphine, fentanyl, oxycodone, codeine), sedative-hypnotics (barbuturates, benzodiazepines, alcohols, zolpidem), cholinergic (organophosphate/carbamate, vinsecticides, pilocarpine, edrophonium), sympatholytics, vphencyclidine. Nystagmus is encountered in patients intoxicated with barbiturates, carbamazepine, phencyclidine, phenytoin, lithium, ethanol, toxalcohols, scorpion stings, and ketamine (9).

Movement disorders: Seizures that may occur as a result of propranolol, lidocaine, sympathomimetics and antidepressants. Tremor caused by lithium, antipsychotics, sympathomimetics, anticholinergics. Rigidity and parkinsonism after antipsychotic drugs, metoclopramide, carbon monoxide, ethylene glycol. Paralysis caused by solvent inhalation such as barium, magnesium, toluene, and heavy metals such as thallium are among the findings that can be detected in cases of poisoning (9).

Mental status changes: In addition to central nervous system depression caused by drugs such as anticholinergic, antidepressant and antipsychotic, agitation caused by amantadine, sympathomimetics, anticholinergic agents, and salicylates are among the findings detected in physical examination (9).

Skin findings: flushing after anticholinergic, boric acid, disulfiram reactions; pale and sweaty skin, which may be caused by sympathomimetic, cholinergic, arsenic and salicylates; cyanosis due to methemoglobinemia or hypoxemia, or desquamation due to heavy metal poisoning such as arsenic and thallium (9).

Blood pressure and heart rate changes: Sympathomimetics, anticholinergics, black widow spider bite, scorpion sting, monoamine oxidase inhibitors, drug withdrawal, hallucinogens and tachycardia and hypertension are seen together. Bradycardia and hypertension occur in poisoning with alpha-adrenergic agonists, sumatriptan, clonidine and cholinergic agents. Tachycardia and hypotension are seen together in beta-adrenergic agonists, disulfiram reaction (late), carbon monoxide, toxic alcohols, colchicine poisoning. Bradycardia and hypertension occur in poisoning with alpha-adrenergic agonists, sumatriptan, clonidine and cholinergic agents. Beta-adrenergic agonists, disulfiram reaction (late), carbon monoxide, toxic alcohols and colchicine poisoning are associated with tachycardia and hypotension. Bradycardia and hypotension occur in beta-blockers, calcium channel blockers, cardiac glycosides, cyanide, opioids, and cholinergic poisonings (9).

Respiratory disorders: While tachypnea occurs as a result of sympathomimetics, central hallucinogens, anticholinergics, and salicylates; Bradypnea occurs due to central nervous system depression as a result of poisoning with opioids, antidepressants, antipsychotics, sympatholytic and cholinergic agents (9).

Physical examination, especially the evaluation of mental status and vital signs, should be repeated frequently (about once every hour depending on the patient's condition) to determine the course of poisoning and the need for further intervention (9).

Electrocardiography

Electrocardiographic (ECG) abnormalities can provide diagnostic and prognostic information. An ECG should be obtained in all patients who are symptomatic or exposed to potentially cardiotoxic agents or unknown substances (15). Particular attention should be paid to the duration of the QRS and QTc intervals. Many drugs cause sodium channel blockade leading to QRS prolongation (e.g. cocaine, tricyclic antidepressants, carbamazepine). Many other drugs cause prolongation of the QT interval by blocking the flow of potassium (eg, most antipsychotics, sotalol). Toxin-induced QRS prolongation in tricyclic antidepressant poisoning requires urgent intervention (9).

Radiographic Studies

Imaging studies are not necessary in every patient but may be useful in some cases (16,17). Heavy metals such as iron, arsenic, drug packages, salicylates, chlorinated hydrocarbons, calcium salts and some poisons can be visualized with plain film radiography. Since agents such as smoke, phosphagen, metal oxides, isocyanates, ammonia, gasoline, kerosene, cyanide, carbon monoxide, phencyclidine, sympathomimetics, ethylene glycol, beta blockers may cause noncardiac pulmonary edema and since they may cause the risk of aspiration after the use of central nervous depressant toxic substances, chest radiography should be performed.

Toxicology Scans (Drug Testing)

Toxicology screening is rarely required in patients who use drugs unintentionally when they are asymptomatic or have clinical findings consistent with their medical history (9). It is recommended to measure acetaminophen and salicylate levels for patients with a history of previous suicidal drug use. It is known that these two agents are quite effective if early treatment is started (9). In a retrospective study, when blood drug levels were studied in patient groups with multiple drug intake, detectable serum acetaminophen levels were found to be high in 9.6 percent of all patients; In a subgroup analysis, almost one-third were found to refuse acetaminophen intake (18). However, positive or negative screening tests cannot definitively detect whether a poisoning is present. A negative test sample may give false negatives because it is below the test threshold. While urine drug levels may be negative in harvests with some toxicity symptoms, it has been found that tricyclic antidepressant (TCA) levels

in the blood are high and false positives occur after taking drugs such as diphenhydramine (19).

Other Laboratory Studies

Serum electrolytes, kidney function tests and glucose measurement should be performed in patients who apply to the emergency department with the complaint of poisoning. In addition to these, serum ketones, creatine kinase, liver function tests, lipase, ionized calcium and magnesium measurements should be performed in those with poor general condition (9). May be useful in certain situations such as serum osmolality in suspected toxic alcohol intake. If possible, a blood pregnancy test should be taken from women of childbearing age if there is no urine. Blood gas, carboxyhemoglobin, and serum lactate measurements may be required in patients with acid-base, cardiovascular, neurological, or respiratory disorders (9). The presence of an anion gap metabolic acidosis may be the first clue to poisoning and should prompt consideration of causes such as salicylates, ethylene glycol and methanol. Serum creatinine, glucose, ketones, and lactate should also be measured to detect other possible causes of anion gap acidosis (9).

POISON MANAGEMENT

Treatment of the poisoned patient depends on the specific poison or poisons involved, the clinical condition of the patient or the risks to life that may occur, and the time elapsed between exposure and arrival at the hospital. Treatment generally includes supportive care, decontamination, antidote therapy, and improved elimination techniques. Help from a medical toxicologist or a regional poison control center can be sought. If possible, it is helpful to contact a medical toxicologist directly (9).

Decontamination

After stabilization of the patient, decontamination should be done. The earlier the decontamination is done, the more effective it will be in preventing poison absorption. Washing with copious amounts of water or saline is recommended for topical exposures. Decontamination of topical chemical exposure should be done before the patient is brought to the emergency room.

For oral intake, vomiting, gastric lavage and administration of activated charcoal are the preferred decontamination methods. vomiting; It is not a common procedure in emergency departments due to the risk of aspiration and delaying the application of activated charcoal. Ipeca syrup and apomorphine used for vomiting are no longer recommended. They are contraindicated especially in the presence of seizures, elderly patients, uncontrolled hypertension, pregnant harvests, and coagulation disorders (20).

Gastric lavage, on the other hand, has considerably reduced its place in emergency practice due to risks such as laryngospasm, hypoxia, and aspiration fluid and electrolyte disorders. However, gastric lavage should be performed only in patients who are suspected of taking a lethal dose of medication, in the intake of drugs that delay gastric emptying (anticholinergics, salicylate, etc.), in exposure to slow-release or enteric-coated drugs, and in cases where activated charcoal is ineffective, even if the patient is asymptomatic, in the first 2-3 hours after intake. It is recommended to be done in (20).

Activated charcoal application is used to prevent the absorption of toxic substances in the stomach and their participation in the circulation. It is recommended to be applied after airway safety is obtained in unconscious and seizure patients. Dose adjustment should be made according to the amount of toxic substance taken. Activated charcoal is contraindicated in patients with intestinal perforation or obstruction, in patients who have taken corrosive substances and at risk of perforation, in poisonings with acidic and alkaline non-absorbent substances, intoxications of carbon and hydrocarbons with low viscosity (20).

Because it reduces intestinal peristalsis, in poisonings with drugs with anticholinergic effects, ' Multiple-Dose Activated Charcoal (MDAC)' is applied at half the dose of the first dose with 2-4 hour intervals following the first dose of activated charcoal. If the half-life of the toxin is long, if the toxic substance is located in the gastrointestinal tract and constantly releases toxin, continuous toxin release due to enteric coated drug or slow release, and if the amount of toxin taken is too high to be absorbed with a single dose of activated charcoal, Multiple-Dose Activated Charcoal are indicated (20)

In certain cases, whole bowel irrigation with oral administration of large volumes of an osmotically balanced electrolyte solution may be performed, endoscopy to remove toxic materials such as drug bezoars and clock batteries, and surgery to remove drug packets.

Antidotes

There are situations where rapid administration of a particular antidote is potentially lifesaving. Antidotes can inhibit absorption, neutralize poisons by binding directly, antagonize end-organ effects, or prevent conversion to more toxic metabolites (9).

Improved Elimination Techniques

Procedures to increase the elimination of toxins include forced diuresis, urinary ion capture, hemodialysis, hemoperfusion, hemofiltration, and exchange transfusion. Various measures may be helpful in selected situations (9).

SUPPORTIVE CARE

Supportive care is the most important aspect of treatment and is often sufficient to allow the patient to fully recover. Supportive care for the poisoned patient is often similar to that used for other critically ill patients, but some issues are managed a little differently:

Protection of the Airway

Airway safety with tracheal intubation should be considered especially in terms of early prevention of complications due to the high risk of aspiration in cases of unconsciousness not due to rapidly reversible causes such as opioid poisoning or hypoglycemia. While it is indicated for tracheal intubation in the presence of severe acid-base disorder or acute respiratory failure, gastric decontamination alone is not an indication. While tracheal intubation with centrally acting neuromuscular blockers may be beneficial in order to protect the patient from acidosis, hyperthermia and rhabdomyolysis in high-grade physiological stimulation, mechanical ventilation should be avoided unless necessary in salicylate poisoning (9).

Hypotension

It should be managed with isotonic intravenous (IV) fluids as initial therapy in hypotensive patients. Vasopressors are required when hypotension does not improve as a result of iv isotonic bolus infusion. In general, direct-acting vasopressors such as norepinephrine or epinephrine are preferred over indirect-acting agents such as dopamine. The superiority of direct-acting agents has been demonstrated in the case of tricyclic antidepressant poisoning (22, 23).

Hypertension

Hypertension in agitated patients is treated with nonspecific sedatives such as benzodiazepines (24). When hypertension requires specific treatment for associated end-organ dysfunction, treatments of choice include calcium channel blockers, phentolamine, labetalol, or nitroprusside. The use of beta-blockers alone is generally not recommended in patients with sympathetic hyperactivity such as cocaine intoxication. Because this can cause unopposed alpha-adrenergic stimulation and intense vasoconstriction (24, 25).

Ventricular Tachycardia

In particular, sodium bicarbonate is the first choice in the treatment of ventricular arrhythmias caused by sodium channel blockade such as tricyclic antidepressants (TCAs), carbamazepine, and cocaine (9). In these cases, the use of Type IA (eg procainamide), IC and III antiarrhythmics is not recommended (9). Isoproterenol may be a good choice in patients with drug-induced torsades

de pointes and prolonged QT interval, and IV magnesium sulfate treatment may be considered in these patients (9). Tachyarrhythmias or bradyarrhythmias due to digoxin toxicity should be treated with digibind.(9).Bradyarrhythmia

Bradyarrhythmias should be treated with atropine and/or temporary pacemarkers. Calcium, glucagon, vasopressor and high-dose insulin therapy may eliminate the need for pacemarkers in the treatment of bradycardia occurring in negative chrontrop intoxications such as calcium channel blockers and beta-blockers. Again, it should not be forgotten that dopamine is effective in the treatment of clonidine-induced bradyarrhythmia (9).

Seizure

In cases of seizures after poisoning, the first choice is benzodiazepines. If there is no response to benzodiazepines, barbiturates can be used as a second option (9). Phenytoin is not used as an antiepileptic in cases of poisoning (26). Again, it should be noted that antiepileptic agents such as levetrecetam may have a low probability of stopping seizures in cases of poisoning (9). Seizure activity resulting from some toskidromas should be treated with antidotes (9).

Agitation

The best agent that can be used in the treatment of agitation resulting from toxicity is benzodiazepines. In cases resistant to benzodiazepines, endotracheal intubation, propofol or phenobarbital are among the options that can be used (9). If agitation develops due to toxidroma, primary treatment should be tried to be treated with antidotes such as physostigmine in anticholinergic toxicity (27).

Hyperthermia

In cases such as serotonin syndrome, toxicity with sympathomimetics or neuroleptic malignant syndrome, secondary hyperthermia may develop. It is obvious that antipyretics such as acetaminophen or ibuprofen are not effective in the treatment. It can be treated with aggressive treatment, especially icy water baths (28). However, in cases of hyperthermia due to complications such as aspiration that may develop as a result of toxicity, classical antipyretics can be used (9).

REFERENCES

1. Toksikoloji Dİ. Diagnosis and treatment in acute poisoning. 2nd Edition *İstanbul Nobel Tıp Kitabevi* 1994;1–10.
2. Kayhan Z. Clinical Anesthesia, Extended 3rd Edition. Istanbul. *Logos Yayincilik* 2004;503–29.
3. Vural NT. Ankara University Faculty of Pharmacy publications. *Ank. 1996 342* 1984;373.
4. Sandilands EA, Bateman DN. The epidemiology of poisoning. *Medicine (Baltimore)* 2016;44(2):76–79.
5. Gummin DD, et al. 2017 annual report of the American association of poison control centers' National Poison Data System (NPDS): 35th annual report. *Clin. Toxicol.* 2018;56(12):1213–1415.
6. Gupta PK. *Fundamentals of toxicology: essential concepts and applications*. Academic Press; 2016:
7. Dart RC, et al. Current pediatric diagnosis and treatment. *Poisoning 18th Ed NY Mc Graw-Hill* 2007;335–360.
8. Özdemir R, Bayrakcı BZ. Hacettepe experience. *Katkı Ped Derg* 2009;31:47–87.
9. General approach to drug poisoning in adults- UpToDatehttps://www.uptodate.com/contents/general-approach-to-drug-poisoning-in-adults?search=approach%20to%20poisining&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1. cited November 23, 2022
10. Akgür SA, Dağlıoğlu N. *Basic Forensic Toxicology*. Akademisyen Kitabevi; 2018:
11. Soslow AR. Acute drug overdose: one hospital's experience. *Ann. Emerg. Med.* 1981;10(1):18–21.
12. Wright N. An assessment of the unreliability of the history given by self-poisoned patients. *Clin. Toxicol.* 1980;16(3):381–384.
13. Monte AA, et al. The accuracy of self-reported drug ingestion histories in emergency department patients. *J. Clin. Pharmacol.* 2015;55(1):33–38.
14. Erickson TB, Thompson TM, Lu JJ. The approach to the patient with an unknown overdose. *Emerg. Med. Clin. North Am.* 2007;25(2):249–281; abstract vii.
15. Yates C, Manini AF. Utility of the electrocardiogram in drug overdose and poisoning: theoretical considerations and clinical implications. *Curr. Cardiol. Rev.* 2012;8(2):137–151.
16. Savitt DL, Hawkins HH, Roberts JR. The radiopacity of ingested medications. *Ann. Emerg. Med.* 1987;16(3):331–339.

17. Kurt TL, Anderson RJ, Reed WG. Rapid estimation of carboxyhemoglobin by breath sampling in an emergency setting. *Vet. Hum. Toxicol.* 1990;32(3):227–229.
18. Sporer KA, Khayam-Bashi H. Acetaminophen and salicylate serum levels in patients with suicidal ingestion or altered mental status. *Am. J. Emerg. Med.* 1996;14(5):443–446.
19. Sorisky A, Watson DC. Positive diphenhydramine interference in the EMIT-st assay for tricyclic antidepressants in serum. *Clin. Chem.* 1986;32(4):715.
20. Tenenbein M, Cohen S, Sitar DS. Whole bowel irrigation as a decontamination procedure after acute drug overdose. *Arch. Intern. Med.* 1987;147(5):905–907.
21. Proudfoot AT, Krenzelok EP, Vale JA. Position paper on urine alkalinization. *J. Toxicol. Clin. Toxicol.* 2004;42(1):1–26.
22. Tran TP, et al. Response to dopamine vs norepinephrine in tricyclic antidepressant-induced hypotension. *Acad. Emerg. Med. Off. J. Soc. Acad. Emerg. Med.* 1997;4(9):864–868.
23. Buchman AL, Dauer J, Geiderman J. The use of vasoactive agents in the treatment of refractory hypotension seen in tricyclic antidepressant overdose. *J. Clin. Psychopharmacol.* 1990;10(6):409–413.
24. Hollander JE. The management of cocaine-associated myocardial ischemia. *N. Engl. J. Med.* 1995;333(19):1267–1272.
25. Lange RA, et al. Potentiation of cocaine-induced coronary vasoconstriction by beta-adrenergic blockade. *Ann. Intern. Med.* 1990;112(12):897–903.
26. Blake KV, et al. Relative efficacy of phenytoin and phenobarbital for the prevention of theophylline-induced seizures in mice. *Ann. Emerg. Med.* 1988;17(10):1024–1028.
27. Burns MJ, et al. A comparison of physostigmine and benzodiazepines for the treatment of anticholinergic poisoning. *Ann. Emerg. Med.* 2000;35(4):374–381.
28. Laskowski LK, et al. Ice water submersion for rapid cooling in severe drug-induced hyperthermia. *Clin. Toxicol. Phila. Pa* 2015;53(3):181–184.

ISBN: 978-625-6955-78-3