TOWARDS THE MULTILEVEL APPROACH IN MEDICAL SCIENCES

Editor: Assist. Prof. Dr. Deniz ÖZBİLİCİ

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Editor

Assist. Prof. Dr. Deniz ÖZBİLİCİ

Authors

Assist Prof. Dr. Deniz ÖZBİLİCİ

Assist. Prof. Dr. Zeynep TANYELİ

Dr. Altay BABACAN

Lect. Dr. Z. Deniz AKTAN

Op. Dr. Felat ÇİFTÇİ

Dr. Emral GÜLÇEK

R.A. Ebru ERTAŞ

R.A. Feride ÇEVİK

Spec. MD. Furkan ASAN

İKSAD Publishing House

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PREFACE

When people imagine the day-to-day activities of health care workers they're usually thinking about the micro level. Common examples of micro-level work include doing certain kinds of mental health or substance abuse treatments in schools, hospitals or even in the military. While micro medical work happens on an individual level, mezzo-level medical work look at groups instead of individuals such as the smallest group family. Since mezzo-level health care work addresses group issues, it is a tool to conduct small institutional, social and cultural changes. Macro-level medical work involves interventions and advocacy on a large scale, affecting communities, provinces or countries. It helps patients via intervening in large systems beyond the access of individuals.

Each article in this book is so valuable for health care workers as each contains carefully prepared extracts of more than one level of fields in medical sciences to assist them in their busy daytime environments.

Assist. Prof. Dr. Deniz ÖZBİLİCİ

CHAPTER 1

ACUTE ABDOMEN SURGERY: A RECENT SHORT REVIEW

Assist Prof. Dr. Deniz ÖZBİLİCİ[1]

[1] Siirt University, Faculty of Medicine, Department Of General Surgery
E-Mail: denizozbilici@yahoo.com

1. Introduction

Acute abdomen is sudden onset of a pain in the abdomen with rapid progression where shock is common. Its management differs due to the complexity of the diagnosis and heterogeneity of pathophysiology. This diseases has a medical emergency which may require immediate surgical intervention. Early diagnosis is critical to avoid unjustified surgical interventions where ultrasonography and tomography may be helpful to assist diagnosis as major options. Use of laparoscopic surgery is popular nowadays. Acute abdomen is clinically important and its common for patients to report to emergency departments.

Acute abdomen is a sudden onset of pain where patient reveals signs and symptoms that has something to do with the viscera of the abdomen. This is a medical emergency as majority of patients are frightened. But only 20-30% of the cases actually need an immediate surgical intervention (Frank, 2021). Acute abdomen management differs because of the heterogeneity of pathophysiology underlying (Djordjevic et al., 2020). Acute abdomen is a common diseases in clinical practice which has acute onset and rapid progression. Electrolyte imbalance or shock is common in this diseases which is needed to be urgently addressed to improve health or save lives of patients Han et al., (2021).

Typical causes of an acute abdomen are diverticulitis, cholecystitis, perforating ulcer, viral or bacterial peritonitis, mesenteric adenitis, sickle cell disease, visceral torsion, and ischemic bowel disease due to atherosclerosis among many others (Alkilany et al., 2021).

The complexity of the diagnosis of abdominal forms of periodic disease often leads to unnecessary surgical intervention. Adherence to the algorithm of diagnosis of periodic disease is required to avoid unjustified surgical interventions (Dyakonova et al., 2016). Ultrasonography helps surgeons arrive to early diagnosis and eliminate alternative diseases and reduce negative laparotomy rate. Ultrasonography is easy, non-invasive, require minimal patient preparation and produce low radiation. It is an important routine diagnostic investigation in acute abdomen patients (Acharya et al., 2019).

Intestinal perforation and mesenteric ischemia are some of the leading causes of morbidity and mortality among the reasons of acute surgical abdomen. Mesenteric ischemia has a mortality rate of 60% and gastric perforation has a mortality of 20-30% (Gupta et al., 2021). Contrast enhanced Computed Tomography is a common imaging test for investigating acute abdominal clinical conditions. It has high sensitivity and specificity and mandatory for correct and prompt diagnosis when life threatening abdominal diseases as mesenteric ischemia are suspected. Contrast medium administration was linked to acute renal failure, therefore radiologist often prefer to perform "Contrast enhanced Computed Tomography" without contrast in patients needing to undergo the exam with increased serum creatinine (De Simone Belinda et al., 2018).

For acute abdomen surgery, anesthesia is essential. Han et al., (2021) studied anesthesia options for clinical patients of acute abdomen

surgery and effect on recovery of gastrointestinal function of patients. They determined that spinal-epidural anesthesia is a good method due to its strengths in gastric function and rates of operation success.

Use of laparoscopic surgery is popular nowadays. It is extended into a diagnostic and therapeutic tool for the management of acute abdominal disease. Therapeutic use of it requires experience, special instrumentation and reliable definite diagnosis. Laparoscopic surgery in acute abdomen is feasible, effective and safe for acute cholecystitis, acute appendicitis and gastroduodenal ulcer perforation. Conflicts in perforated diverticular disease and small bowel obstruction exist. For purulent peritonitis, attention is needed to avoid residual abscess formation and sepsis by thorough irrigation of the peritoneal cavity and on time antibiotic therapy. The proper indication for each case under the certain emergency circumstances is crucial (Pavlidis et al., 2015). Nowadays, nearly all abdominal operations are performed laparoscopically, and this made its application to the emergency abdominal surgery possible (Robaina et al., 2018).

Risk factors related with poor outcomes in patients receiving emergency surgery were investigated by Maeda et al., (2015). Surgical Apgar Score (SAS) was revealed as independent predictor of the death. SAS, duration of the surgery and preoperative Sequential Organ Failure Assessment (SOFA) were identified as independent predictors of the complication. SAS and preoperative SOFA were found as useful to predict poor prognosis after emergency surgery due to acute abdomen.

The safety and feasibility of laparoendoscopic single-site surgery estimated and obstetric and neonatal outcomes of single and multiport procedures were compared by Jiang et al., (2021) in pregnant patients underwent laparoscopic surgery during their pregnancy. Feasibility and efficacy of laparoscopic surgery during pregnancy was similar for singleport or multiport routes. Whereas, singleport route was found associated with less postoperative pain, lower anxiety and shorter hospital stay.

Acute cholangitis and acute cholecystitis are widespread acute abdomen in biliary surgery. The morbidity of acute cholecystitis is high, and abdominal ultrasound is the first choice for imaging. For mild acute cholecystitis, early laparoscopic cholecystectomy is the first choice. For patients with severe acute cholecystitis, supportive treatment is needed to improve symptoms for elective cholecystectomy. For severe cholecystitis patients who can not tolerate surgery risk, gallbladder drainage should be performed in time. Acute cholangitis mortality is high. Magnetic resonance cholangiopancreatography is an important imaging application. Early biliary decompression, antibiotic application and general supportive treatment are treatments of acute cholangitis. Common methods of biliary decompression are percutaneous transhepatic cholangiography drainage, endoscopic endoscopic ultrasound-guided biliary drainage, duodenal papillary bile duct drainage and surgical placement of T-tube drainage (Wu & Tang, 2021).

Instead of increasing number of bariatric procedures worldwide, a consensus or guidelines related to the emergency management of long-term complications after bariatric surgery are not available. De Simone et al., (2020) investigated the emergency surgeon approaches and their personal experiences related to this group of patients by using a web survey to highlight current management techniques in emergency. Data collected by international web survey including 117 emergency surgeons answering 26 multiple choice and open questions. Researchers concluded that, emergency surgeons must be careful for complications of postoperative bariatric surgery. CT scan with oral intestinal opacification carefully applied by the radiologist and the surgeon can be useful in diagnosis. For inconclusive clinical and radiological findings, if symptoms fail to improve, surgical exploration for bariatric patients presenting acute abdominal pain, by laparoscopy if expertise is available, is mandatory in the first 12–24 h, to have good outcomes and decrease morbidity rate (De Simone et al., 2020).

Acute abdomen treatment during chemotherapy is difficult due to the complex status of patients. At least three predictive factors is related to in-hospital death following emergency surgery of chemotherapy recieving patients. These factors are, older age, poor performance status and low serum albumin level (Maeda et al., 2020).

A study was conducted by Zeb et al., (2018) in a hospital in Pakistan in Peshawar to determine frequency and conversion reasons of laparoscopic procedure into open surgery. 10% of laparoscopic procedures were found converted into open procedures. Reasons of

conversion into open surgery in case of acute abdomen were determined as 1) adhesions, 2) previous abdominal surgeries, 3) severity and time of presentation of perforations, 4) severe inflammation, 5) severe bleeding and 6) difficulties in visualization of anatomy.

Emergency surgery outcomes for acute abdomen are better for non-dialysis patients than for dialysis patients. Long-term dialysis often causes metabolic and physiological problems affecting the outcomes of surgery. Immediate diagnosis, onset of the most suitable surgical procedure, and meticulous postoperative cares are required to improve surgical outcomes of dialysis patients (Tomino et al., 2014).

Congenital accessory spleen or splenunculi is a small mass of splenic tissue that failed to fuse with the primary spleen during embryogenesis. Splenunculus is generally asymptomatic and diagnosed in many cases by coincidence during the abdominal imaging, necropsy or laparotomy. It rarely present acute abdomen in case of infract or torsion. Some reports of malignant changes in the accessory spleen are also exist. Surgeons must to be aware of these small masses (splenic tissue) at splenectomy. It can lead to recurrence of hematological disorders if left unnoticed after total splenectomy (Kar et al., 2021).

Tuberculosis is one of a main public health problem globally. This dieseases may be confused with different diseases which frequently delay diagnosis. Abdominal tuberculosis includes involvement of the gastrointestinal tract, peritoneum, solid organs and lymph nodes which accounts 5% of tuberculosis cases. Tuberculosis is great imitator and can masquerade as cancer. Most tuberculous patients misdiagnosed as

cancer have wide neoplastic lesions which suggest an advanced staged malignancy (Meregildo-Rodriguez et al., 2021).

Nutritional side effects and mineral and vitamin deficiencies may be produced by bariatric surgery. A part of these problems can give rise to acute manifestations that could be evaluated for the first time by the emergency health services. In particular, some of them can present with acute abdominal symptoms that can mimic acute surgical problems ("false acute abdomen"). The most frequent nutritional problems giving rise to acute abdominal symptoms in post-bariatric patients are thiamine deficiency and dumping syndrome. Special emphasis given to clinical history and presenting symptoms can help to make correct differential diagnosis, escape for costly, time-consuming and invasive diagnostic tests and examinations (Busetto, 2020).

Half of the elderly undergoing emergency abdominal surgery are malnourished. Surgical nutritional access receiving elderly have lower rates of mortality and gastrointestinal complications (Gogna et al., 2021).

2. Emergency service

Acute abdomen is clinically important and pain in the abdomen is a chief feature which result with very common for patient to report to emergency departments. Illnesses of 'acute abdomen' vary from mild to sever and management vary from symptomatic relief to emergency operative intervention. To formulate a management plan in limited time is a significant challenge for the clinician (Kumar & Ray, 2021).

Covid-19 infection is a reason for abdominal pain and must be considered in different diagnoses of acute abdomen in surgical wards. Oncological patients are one of vulnerable groups. Increased rate of patients with colorectal cancers neglected therapeutically or uninvestigated during the pandemic period who presented emergencies for complications like occlusion or tumor perforation. Personal protective equipment and strict rules of asepsis and antisepsis are required to prevent transmission of infection in hospital (Serban et al., 2021).

Some patients with COVID-19 suffer from acute abdomen who require surgical treatment but there is no treatment consensus for these types of patients. Emergency surgery improve outcomes of acute abdomen covid patients but also patients benefit the resolution of pulmonary inflammation (Zhao et al., 2020).

Timing of surgery is important for prognosis. In acute abdomen patients, surgery timing is more important but early emergency surgery is frequently logistically scaring due to constraints of operating room, anesthesiologist and nurse support. For appendicitis and for peptic ulcer perforation, surgery within 24 hours from symptom onset is recommended. But at other acute abdomen disease, consensus is not so strong. If surgeon have many emergent patients and resources are limited, priorities must be decided for surgery and an emergency triage is needed. Many triage systems exist in the literature but there is a few controversy. Resources utilization will be more efficient and acute care

surgery might be performed in ideal time when a triage system is followed (Kim et al., 2016).

Due to Covid-19 pandemic, the triage, assessment and management of patients at critical conditions in emergency department has become challenging. In many cases, Covid-19 clinical features are heterogeneous and subtle which easily may be overlooked in case of other acute diseases. Gastrointestinal symptoms are common in patients with Covid-19 as coronavirus have ability to enter gastrointestinal epithelial cells. However, these complaints can also be caused by a Covid-19-independent concomitant abdominal pathology. Therefore, patients with acute abdominal pain and fever need to be assessed very thoroughly (Kühn et al., 2020).

Artificial intelligence and machine learning are promising applications for medical diagnosis, imaging and laboratory testing procedures and can also be used in acute abdomen surgery (Fraiwan et al., 2020). Major limitations for the usage of robotics in emergency setting are elevated cost of platform and training requirement for the entire surgical team, anaesthesiologists and operative nurses (Petz et al., 2021).

3. Conclusions

Early diagnosis is critical to avoid unjustified surgical interventions where ultrasonography and tomography may be helpful to assist diagnosis as major options. Use of laparoscopic surgery is popular nowadays. Acute abdomen is clinically important and its common for patients to report to emergency departments. Typical causes of an acute abdomen are diverticulitis, cholecystitis, perforating ulcer, viral or

bacterial peritonitis, mesenteric adenitis, sickle cell disease, visceral torsion, and ischemic bowel disease due to atherosclerosis. Surgical Apgar Score and Sequential Organ Failure Assessment are useful to predict poor prognosis after emergency surgery due to acute abdomen. Surgical nutritional access receiving elderly have lower rates of mortality and gastrointestinal complications.

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CHAPTER 2

INNOVATIVE WOUND CARE AFTER SURGERY

Assist Prof. Dr. Deniz ÖZBİLİCİ[1]

[1] Siirt University, Faculty of Medicine, Department Of General Surgery
E-Mail: denizozbilici@yahoo.com

1. Introduction

Surgical wounds are applied specifically for medical or diagnostic aims. Wound infections are among common and significant burden to patient and healthcare systems. Surgical site infections are an indicator of the quality of care in hospitals. Different types of wounds require different care approaches where surgical wound care requires an multidisciplinary approach. When caring for surgical wounds, primary protection against inner and outer microorganisms is importamnt. Usage of novel nanomaterials and nanotechnology for the biomedical applications is sharply increasing with increasing numbers and types of surgical wound care products. Many innovative products exist on market and some are mentioned here below after presentation of general inromation on the wound and surgical wound subjects.

Wound is the defect of skin and subjacent tissues as a result of many possibile factors. Wounds can be classified as acute and chronic; or cut, chopped, scalped, stabbed, torn, bruised, bitten, surgical and gunshot. Surgical wounds are applied specifically for medical or diagnostic aims in aseptic conditions with minimum tissue damage in anesthesia conditions with hemostasis by separating anatomical structures with sutures (Kovalenko, 2020).

Surgical site complications of wound infections are among main burden to healthcare systems (Schurtz et al., 2018). Surgical site infections are an indicator of the quality of care in hospitals (Gillespie & Chaboyer, 2018). The increasing numbers of surgeries involving high risk, multimorbid patients, coupled with inconsistencies in the practice of

perioperative surgical wound care, increases patients' risk of surgical site infection and other wound complications (Gillespie et al., 2021).

Wound care is not just changing the dressings. Different types of wounds require different care approaches. Optimal care supports the tissue's natural healing process effectively and gently (Kovalenko, 2020). Wound infections can be exogenous or endogenous bacteria sourced. Wound infection probability mostly depends on systemic host defense of patients, local wound conditions and microbial load. Instead of modern surgical methods and usage of antibiotic prophylaxis, surgical site infections are among the most common complications encountered in surgery. It effects both patients and health systems thus a major cause of morbidity, prolonged hospital stay and increased health costs (Bhumbla et al., 2019).

Surgical wound care requires an interprofessional approach; however, there is considerable variation in practice and a lack of robust evidence to guide clinicians (Gillespie et al., 2020). Given the tremendous medical, social and financial costs of surgical site infections, the pressure to minimize these complications has been mounting (Khalafallah et al., 2021). Using an evidence-based and standardised approach to surgical wound management will reduce patients' risk of wound-related complications (Walker et al., 2021).

Types of wound healing include primary tension healing, delayed primary tension healing, secondary tension healing, and scab healing. When caring for surgical wounds, primary protection against microorganisms is important. In this case, sterile dressings play an

important role (a medical surgical patch with an absorbent pad). The pad is characterized by high hygroscopicity, does not stick to the wound and does not leave fibers in the wound. The frequency of dressings changing depends on the healing process and the amount of exudate released from the wound. For festering wounds, the dressing should be changed daily and sometimes more often. Hands and gloves should be worn before bandaging. After removing the gloves, the hands are also treated with an antiseptic. Sutures from the surgical wound are removed after the onset of epithelialization, when the wound is covered with a thin protective film. However, in this period there are still wound channels from the threads, so after that it is necessary to treat the wound several times with antiseptic. Signs of local infection of the wound are redness, excess exudate, sometimes – with the addition of pus, odor, pain in the area of injury, fever, edema. Sometimes postsurgical wound suppuration occurs even with proper care due to weak immunity or rejection of surgical suture material. If there is suppuration, it is advisable to switch to dressings with Dekasan and hyperosmolar antibacterial ointments. Unlike 2 % povidone-iodine, which causes severe inhibition of granulation in an open wound, Dekasan does not damage granulation tissue. Surgical treatment, lavage, drainage, antibiotics, laser or ultrasound may also be required. After removing the signs of local inflammation, secondary sutures are applied to the wound or the edges of the wound are connected with the help of adhesive plaster. Before starting the wound care procedure, it is necessary to assess the condition of the wound bed, the nature of the

exudate, the condition of the tissues around the wound, pain, wound size (Kovalenko, 2020).

Most of the surgical wounds are closed (with sutures or staples etc) and heal by primary intention. If closure is not possible, or the wound breaks down, wounds may be left to heal from the bottom up (healing by secondary intention). Healing of surgical wounds by secondary intention are significant challenge. Many times, additional treatments are required during healing, significant financial burden is related with with treatment of these wounds. Negative pressure wound therapy is increasingly getting used for surgical wound healing via secondary intention. This type of wound dressing system provides a vacuum (negative pressure) to the wound to remove fluid into the canister to be conducive to wound healing. Use of negative pressure wound therapy as a treatment for surgical wound healing by secondary intention has been rapidly increasing despite there being limited high-quality evidence to support its clinical and cost-effectiveness. Given the increasing use of this device in routine care, a full and sufficiently powered randomised controlled trial is essential to evaluate the effectiveness of this treatment for surgical wound healing by secondary intention (Chetter et al., 2021).

Wound management should be conducted with a multidisciplinary approach. As an example, an endocrinologist, a diabetic foot specialist, a purulent surgery surgeon, a vascular surgeon, and a nurse are involved in the treatment of ulcerative defects in patients with diabetes. Treatment of wounds is necessary to maintain a humid environment in

the wound, maintain a constant temperature without hypothermia, provide adequate drainage and not too tight tamponade, use additional means of healing (Kovalenko, 2020).

Wound healing has relation with patient nutritional status and local factors. Wound infection and disruption significantly increases the mortality and morbidity of malnourished group patients. Socio economic status and wound healing has indirect correlation. Malnourishment has a definite effect on the process of wound healing (Singh et al., 2019).

1. Innovative approaches

Most surgical cuts heal by primary intention (wound edges are apposed with sutures, clips or glue). But some heal by secondary intention (open wound heals by granulation tissue formation). Evidence regarding the epidemiology, management, and impact on patients' quality of life of these surgical wounds healing by secondary intention is lacking. This is resulting with uncertainty of effective treatments and with difficulty in planning care (Chetter et al., 2019).

Implementation of novel nanomaterials to biomedical applications is providing non-toxicity and biocompatibility in the human biological systems (Wang et al., 2018).

Hypochlorous acid is a natural molecule produced by immune system which is very active against fungal, bacterial and viral microorganisms. Hypochlorous acid prevent biofilm, improves oxygenation condition of wound and improve healing. But natural hypochlorous acid is unstable.

Technology can help to stabilize it into topical antiseptic agents to provide optimal healing environment for wounds; combining with silicone may be ideal for reducing scarring (Gold et al., 2020).

"Curcumin loaded chitosan/poly ethylene glycol nanomaterial" could be promising candidate to prevent microbial infections in wound, healing wound rapidly and inhibit the proliferation of apoptotic cells. Thus, "Curcumin loaded chitosan/poly ethylene glycol nanomaterial"could be a potential therapeutic agent with broad spectrum applications in the future. The growth of *S. aureus* and *E. coli* were inhibited mostly by "chitosan/poly ethylene glycol nanomaterial" treatment. "Curcumin loaded chitosan/poly ethylene glycol nanomaterial" showed complete tissue regeneration in wound excised mice (Chen et al., 2021).

Lignin-loaded nanoparticles can be used for wound healing. Dextran/glycol membranes loaded with lignin were fabricated and examined on wounds by Dai et al., (2021). Wounds of mouse was quick healed by the lignin-loaded dextran/glycol nanoparticles with fewer injury. As a results of the study, lignin-loaded dextran/glycol nanoparticles-based dressing material was found a ground-breaking nanomaterial for wound repair and implantations for wound injury in anorectal surgery.

A study was designed by Cao et al., (2021) to establish the composition of wound bandages based on Cerium nanoparticle-loaded polyvinyl alcohol nanogels. The Cerium nanoparticle nanogel was fabricated by

the fructose-mediated reduction of Cerium oxide solutions within the polyvinyl alcohol matrix. *In vivo* healing of skin wounds formed in mouse models over 24 days. In contrast to the untreated wounds, rapid healing was perceived in the Cerium nanoparticle nanogel-Glu-treated wound with less damage. Findings indicate that Cerium nanoparticle nanogel-Glu-based bandaging materials could be a potential candidate for wound healing applications in the future.

Advanced biomedical curcumin nanoparticles combined with a copolymeric matrix that had a dual function were developed and shown to promote antiinflammatory, functional recovery, and successful neuroprotective effects in a study of Liu et al., (2021). The application of curcumin nanoparticles packaged in a thermoresponsive drug carrier device improves sustainability, bioavailability of blood, longevity, and biocompatibility. This nanocomposite showed enhancement of neuroprotection, axonal growth performance, and theoretically, functional recovery at the location of femoral fracture injury, by curcumin-primed polycaprolactone. In addition to these membranes being used at different temperatures, they improved the drug charge films and exhibited better-regulated release profiles for curcumin. These data provide a simple hybrid clinical approach for the prevention and rehabilitation of femoral fractures in humans.

Wang et al., (2021) designed and synthesized highly porous alginate and gelatin hydrogels with zinc oxide nanoparticles as dressings using sol–gel methods. The alginate and gelatin hydrogels with zinc oxide nanoparticles demonstrated enhanced inflammatory and antibacterial

properties. *In-vivo* examinations showed that the composition of the synthesized alginate and gelatin hydrogels with zinc oxide nanoparticles enhanced wound healing and promoted rapid cell construction and growth. Therefore, the alginate and gelatin hydrogels with zinc oxide nanoparticles strategy promotes the future application of these nanoformulation hydrogels for wound bandaging in fracture surgeries.

In research of Wang & Zhang, (2021), a thermo-sensitive copolymer PNIPAAm-co-MHq was used to successfully synthesize different nano sizes silver nanoparticles in the ranges between 1.5 to 4 nm with uniform dispersion. The polymeric assisted synthesized Ag nanoparticles (AgNPs@PM) exhibited reasonable solution stability and thermalresponsive behaviour. In specific, AgNPs@PM_3 (1.59 nm) displayed improved bacterial resistance against clinically approved anti-biotic resistant bacterial pathigens with very low MIC value (4.05 μg/mL). Subsequently, the thermal responsive polymeric molecular structure on AgNPs synthesis has been established that significant temperature dependened anti-bacterial efficiency. It was also observed that the nonparticipants size, temperature responses and proportion of thermosensitive copolymer also influenced the antibacterial efficacy of AgNPs@PM. Resulting thermal sensitive polymer nanocomposite can be extremely beneficial for wound healing treatment after femoral fracture surgery.

Sessile bacteria can produce extracellular polymeric substance as protective barriers from host immune defenses and antimicrobial agents

and thus, can be exceedingly difficult to eradicate. A novel wound care gel that disrupts the extracellular polymeric substance and destroys the inciting pathogens has been developed for the treatment and prevention of biofilm-related infections. This is achieved by the simultaneous action of four key ingredients: 1) citric acid; 2) sodium citrate; 3) benzalkonium chloride; 4) polyethylene glycol. These constituents together create a high osmolarity, pH-controlled environment that deconstructs and prevents biofilm formation, while destroying pathogens and promoting a moist environment for optimal wound healing (Salem & Mont, 2021).

Novel the bilayered electrospun biosheet with rapid cell mimiciking and proliferative efficacy will be suitable for wound healing application. The optimized concentration of gelatin (G) and sodium alginate (A) biosheet with nanofibrous Poly (3-hydroxybutyric acid) (P) as a bilayered elctrospun matrix through electrospinning. The engineered GAP bilayered biosheet involves tissue formation at extra cellular matrix (ECM) which further characterized its function *in vitro* and invivo. Fabricated GAP exhibit better physiochemical properties, biological and mechanical properties with superior prosomes and enhance air passable at skin wounds. The Bilayered biosheet matrix possess better biocompatibility, cell adherence, fructuous and cell to cell interactions evaluated using cell lines. Furthermore, GAP bilayered matrix regulates growth factors to attain maximum wound closure efficiency during invivo. Thus, the fabricated GAP electrospun biosheet would be a possible wound dressing for skin wound applications (Jiang et al., 2020).

Growing multidisciplinary field of tissue engineering aims to regenerate, improve or replace predictably damaged or missing tissues for a variety of conditions caused by trauma, disease and old age. To ensure that tissue engineering methods are widely applicable in the clinical setting, it is necessary to modify them in such a way that they are readily available and relatively easy to use in daily clinical routine. Therefore, the steps between preparation and application must be minimized and optimized to make them realistic implementation (Crisci et al., 2019).

Surgical nursing practice is constantly changing due to the increasing complexity of surgical wounds; the increasing numbers and types of surgical wound care products, and the comorbidity, complexity and advancing age of surgical patients (Mutford, 2018).

2. Conclusions

Innovative products containing nanoengineering solutions are fast developing and promising to heal vounds without infection. Global market scanning of commercial nanomaterials designed for wound healing may help to improve speed and success of wound healing stages of patients with lower costs compared to repeated medical interventions.

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CHAPTER 3

BENIGN CHILDHOOD EPILEPSY: A RECENT REVIEW

Assist. Prof. Dr. Zeynep TANYELİ[1]

[1] Siirt University, Faculty Of Medicine, Department Of Pediatric Health And Diseases
E-mail: zeynep_tnyl@hotmail.com

1. Introduction

Epilepsy is a highly dynamic disorder in neurology. It is among the common neurological conditions in children. Drug resistance in epilepsy impacts life of children and families. Epilepsy is associated with a wide spectrum of comorbidities in children including anxiety, depression, autism disorder, attention deficits, sleep disorder, migraine and cognitive impairment. “Childhood absence epilepsy” and “Benign childhood epilepsy with centrotemporal spikes” are the most common childhood epilepsy syndromes and they share a similar age-dependence. Among them, benign childhood epilepsy with centrotemporal spikes is the main epilepsy syndrome in children. Behavioral disorders present in one-third of patients with benign childhood epilepsy with centrotemporal spikes. Instead of its prevalence, this type of epilepsy is often missed entirely or misdiagnosed. Atypical benign partial epilepsy is a special type of epileptic syndrome in children with combination of epileptic negative myoclonus, focal motor seizures, atypical absence seizures and continuous spike wave during slow sleep. Further investigation into, the spectrum of benign children epilepsy are needed

Neurological and psychiatric disorders are related with pathological neural dynamics. The underlying patterns of cell-cell communication networks resulting with emergence of pathological dynamics remain unknown (Hadjiabadi et al., 2021). Malformations of cortical development indicate many neurodevelopmental disorders as common causes of epilepsy (especially refractory childhood epilepsy) (D’Gama

& Poduri, 2021). Epilepsy is a highly dynamic disorder in neurology. Random seizures are characteristic sign of epilepsy but for centuries, researchers looked for temporal organization patterns in occurrence of seizure. Chronic recordings of human brain activities produced evidence for the epileptic brain activity cycles operate at different timescales such as circadian (daily), multidien (multi-day) and circannual (yearly) (Karoly et al., 2021).

Epilepsy is a common chronic neurological disorder at prevalence of 0.5–1%. Current epilepsy treatments are mainly based on symptomatic therapies. Patients without adequate response to drugs are defined as pharmaco-resistant. More than 20 antiseizure medications availabile but 1/3 of epilepsies are drug-resistant. Heterogeneity of seizures, heterogeneity of epilepsies, comorbidities, wide spectrum of efficacy and safety of antiseizure medications make management of these patients challenging (Fattorusso et al., 2021).

Literature related to epilepsy with positive neural autoantibody has expanded during last decade. Increased interest exists among clinicians to identify potentially treatable causes of refractory seizures. Range is wide for reported neural autoantibody positivity rates among epilepsy populations. Highest frequency reported in individuals with focal epilepsy of unknown cause and new-onset seizures. In some cases, significance of antibodies are uncertain (Steriade et al., 2021).

In 70-90% of children having tuberous sclerosis complex develops epilepsy which is often medication resistant (Kotulska et al., 2021).

Development of antiseizure drugs is in great progress (with diverse molecular targets). Despite that, more than 1/3 of epilepsy patients continue to show resistance to antiseizure drugs. This condition is named as pharmacoresistant epilepsy. Pharmacoresistant epilepsy management involves significant challenges. Promising advances were made for using interdisciplinary techniques in the past decade involving bioinformatics, biophysics, biochemistry and biomaterials. This allowed high precision prognosis and development of different drug targets for pharmacoresistant type of epilepsy. Novel tools named as viral vector gene delivery, chemogenetics and optogenetics were provided promising approaches for the precise treatment of this type of epilepy (Xu et al., 2021).

Epilepsy is a common neurological problem in children. Many of the children with epilepsy respond to drugs but 30% of children are drug resistant. Drug resistant epilepsy is has serious consequences with high mortality and adverse cognitive outcomes. Drug resistant epilepsy effects life of child and caregivers (Kumar, 2021).

Epilepsy is increasingly associated with a wide spectrum of comorbidities. Epileptic seizures are essential part of childhood epilepsy. Many mental health, neurological and cognitive disorders add burden to childhood epilepsy disease and decrease quality of life. Frequent comorbid conditions in epilepsy of children are anxiety, depression, autism spectrum disorders, attention deficits, sleep disorders, migraine and cognitive impairment. Most of the drugs used for comorbid conditions are safe and do not lower seizure threshold but

the evidence showing drugs are effective in treating many of the childhood comorbidities of epilepsy is quite limited (Holmes, 2021).

In contrast to adolescents epilepsy and adults epilepsy, neonatal seizures and early age epilepsy has specific challenges such as low choices for treatment. Also high seizure burden and epileptic encephalopathy gets associated with behavioural, developmental and cognitive problems. Reasons include etiology, epileptic encephalopathy, seizure burden and antiseizure medication. Opposite of adults and older children, few drugs are licenced for infants (Pressler & Lagae, 2020).

2. Benign childhood epilepsy with centrotemporal spikes

The most common epilepsy syndrome in childhood is benign childhood epilepsy with centrotemporal spikes which accounts for 14–17% of children epilepsy cases (Wu et al., 2021a). These children having benign childhood epilepsy with centrotemporal spikes experience many cognitive impairments (Zhang et al., 2020). They have lower language skills compared to their peers and show difficulties in semantics and syntax domains (Teixeira et al., 2020).

Cortical gyrification, aberrant cortical thickness and sulcal depth in areas related to cognitive functions such as attention, memory and language, and also correlation between brain regions and verbal intelligence quotient and diseases onset age are potential markers in benign childhood epilepsy with centrotemporal spikes (Li et al., 2020).

Approximately 1/3 of patients with benign childhood epilepsy with centrotemporal spikes experience behavioral disorders. Early aged seizures and bilateral interictal epileptic discharges are risks for behavioral disorders in benign childhood epilepsy with centrotemporal spikes (Özgen et al., 2021).

To reduce benign childhood epilepsy with centrotemporal spikes associated cognitive and behavior problems it is esential to select drugs which cause psychosocial effects and impair cognition, and drugs improve quality of life. Oxcarbazepine is a safe drug which does not impair neuropsychologic functions, without mood burden in children. Oxcarbazepine has positive effects on perception of quality of life, happiness and life satisfaction in children (Liu et al., 2020).

"Childhood epilepsy with centrotemporal spikes" is also known as "benign epilepsy with centro-temporal spikes" or "Rolandic epilepsy". It is often misdiagnosed or entirely missed due to nocturnal and brief seizures and difficulty in identifying during electroencephalogram. Brain activity detection is significantly associated with this epilepsy type; awake electroencephalogram may improve diagnostic screening of it and may help to predict clinical outcomes. Epileptic zone in this epilepsy patients exhibit lower complexity where these nonlinear measures can be a screening tool (Sathyanarayana et al., 2020).

There is not any specific guideline for the treatment of benign childhood epilepsy with centrotemporal spikes. Levetiracetam, sodium valproate, carbamazepine, lamotrigine and oxcarbazepine are recommended in many countries as first-line drugs. But a few of these drugs are related

with cognitive decline. Monotherapy, particularly levetiracetam monotherapy is a well first-line therapy to normalize electroencephalograph and prevent cognitive declines. Polytherapy is recommended to be avoided, mostly the administration of sodium valproate relates with poor cognition (Kessi et al., 2021).

In the study of (Wu et al., 2021a), new diagnosed patients of "benign childhood epilepsy with centrotemporal spikes" show emotion discrimination dysfunction (sadness, fear and disgust) which is severe for younger age onset. After epilepsy remission, ability to discriminate emotions returnes to normal.

Although the accuracy of attention network test in benign childhood epilepsy with centrotemporal spikes patients after remission was correlated with age of onset and total number of seizures, benign childhood epilepsy with centrotemporal spikes patients had no attention network damage after complete remission compared with healthy controls (Wu et al., 2021b).

The pathogenesis of benign childhood epilepsy with centrotemporal spikes is unknown, but it is thought that genetic factors play a role in susceptibility to the disease (Shi et al., 2020).

RYR2 gene (encodes ryanodine receptor 2 protein) is potentially a candidate pathogenic gene (mainly located on endoplasmic reticulum membrane) of benign epilepsy of childhood with centrotemporal spikes. More attention should be paid to epilepsy patients with *RYR2* mutations, which were associated with arrhythmia and sudden unexpected death in previous reports (Ma et al., 2021). Genetics

is an important factor in benign epilepsy of childhood with centrotemporal spikes pathogenesis, and <10 genes were associated with benign epilepsy of childhood with centrotemporal spikes (Neng et al., 2020).

Benign childhood epilepsy with centrotemporal spikes risk is substantially increased by maternal smoking around birth (Shi et al., 2020).

Benign partial epilepsy with centrotemporal spikes (BECTS) with attention-deficit hyperactivity disorder (ADHD) has the characteristics of early age of onset, long course of disease and low intelligence score. In addition, the epileptiform discharges of BECTS-ADHD were prone to be bilateral or diffuse, and polypharmacological treatment is also common in this group (Huang et al., 2020).

In children with benign childhood epilepsy with centrotemporal spikes cognitive impairment has complex etiologies (associated closely with abnormal neural networks). Brain structure and function multimodal magnetic resonance imaging is a strong tool for exploring abnormal neural networks of cognitive impairment in epilepsy. It helps to study the pathogenesis of epilepsy at the brain structure and function level via analyzing images (Tan et al., 2020).

The magnetic source inactivation of the medial frontal cortex and posterior cingulate cortex regions during the interictal time may be the reason for cognitive decline in early untreated children with Benign partial epilepsy with centrotemporal spikes. Children with benign partial epilepsy with centrotemporal spikes with cognitive decline had

a longer course of epilepsy and more seizures. The magnetic source localization in the 4–8 Hz frequency band may be a new imaging marker for the diagnosis of new benign partial epilepsy with centrotemporal spikes (Li et al., 2020).

Magnetoencephalography could reveal the aberrant neural activities in benign childhood epilepsy with centrotemporal spikes patients during the interictal period, and such abnormality is frequency-dependent. Gamma oscillations could be used to identify benign childhood epilepsy with centrotemporal spikes patients without interictal epileptiform discharges (Zhang et al., 2020).

"Benign childhood epilepsy with centrotemporal spikes" and "Childhood absence epilepsy" are the most common childhood epilepsy syndromes and they share a similar age-dependence. However, the two syndromes clearly differ in seizures and electroencephalogram patterns. There are grey matter volume differences between childhood absence epilepsy and benign childhood epilepsy with centrotemporal spikes. Grey matter volume in childhood absence epilepsy significantly decreases in the areas of right inferior frontal and anterior temporal compared to benign childhood epilepsy with centrotemporal spikes and controls. Grey matter volume differences may suggest that there may be localized, specific differences in brain structure between these two types of epilepsy (Fujiwara et al., 2020).

There may be an association between interictal electroencephalogram abnormalities and the duration of seizure in benign childhood epilepsy

with centrotemporal spikes, indicating that interictal EEG abnormality may be a target for treatment (Yamamoto et al., 2020).

3. Atypical forms of benign childhood epilepsy

Atypical benign partial epilepsy of childhood is a special type of epileptic syndrome which has combination of epileptic negative myoclonus, focal motor seizures, atypical absence seizures, and a continuous spike–wave during slow sleep. Although the seizures are resistant to antiseizure drugs effective for focal epilepsy, they are markedly responsive to ethosuximide. An incorrect antiseizure drugs choice may aggravate the seizures and continuous spike–wave during slow sleep, resulting in a pseudo-catastrophic state or nonconvulsive status epilepticus (Nishikawa et al., 2020).

Benign childhood epilepsy with centrotemporal spikes outcomes are frequently very good, but a few atypical forms (especially electrical status epilepticus in sleep) have worse outcomes and negative impacts on cognitive development. Children with benign childhood epilepsy with centrotemporal spikes with electrical status epilepticus in sleep shows altered brain activity in the central executive network and salience network. Difference of impairment in the central executive network and salience network may help to understand underlying neuropathophysiology (He et al., 2020).

"Benign childhood epilepsy with centrotemporal spikes" is has less typical clinical presentations which can lead to misdiagnosis or wrong treatment. Further investigations on this epilepsy are required (Zhao et al., 2017).

4. Conclusions

"Benign childhood epilepsy with centrotemporal spikes" is the most common and "Childhood absence epilepsy" is the second most common childhood epilepsy syndrome for children. Behavioral disorders are frequent of benign childhood epilepsy with centrotemporal spikes patients. Atypical benign partial epilepsy of childhood is a special epileptic syndrome type with combination of atypical absence seizures, epileptic negative myoclonus, a continuous spike–wave during slow sleep and focal motor seizures.

Detecting brain activity that is highly associated with benign childhood epilepsy with centrotemporal spikes. Magnetic source localization in 4–8 Hz frequency band can be a new marker for imaging and new diagnosis of benign partial epilepsy with centrotemporal spikes.

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CHAPTER 4

PEDIATRIC ORGANOPHOSPHATES TOXICITY: A RECENT REVIEW

Assist. Prof. Dr. Zeynep TANYELİ[1]

[1] Siirt University, Faculty Of Medicine, Department Of Pediatric Health And Diseases
E-mail: zeynep_tnyl@hotmail.com

1. Introduction

Organophosphate esters causes many diseases as endocrine disruptors via human exposure. These synthetic chemicals are in highest concentrations in closed indoor environment as they are used as plasticizers and flame retardants which they leach from consumer products. Cloth textiles, home furnishings, curtains, carpets, construction materials, electronics, processed foods and children's products contain them as additives. Children are more vulnerable than adults due to proximity to dust, high level of hand to mouth activity and being at critical neurodevelopment period. Associated health risks are allergies, inflammation, oxidative stress, neurotoxicity, endocrine-disrupting, behavioral development problems, adversely impacted fine motor skills and early language abilities; homeostasis of sex steroid hormones and pregnancy outcomes etc.

Here in this review, some latest studies related to the effects of organophosphate esters on pediatrics are reviewed.

Environmental pollution is a public health concern. As endocrine disruptors, organophosphates esters causes many diseases due to different levels of human exposure (Liu et al., 2021). Organophosphate esters are in focus of environmental science due to their large production volume, wide application range, presenting everywhere, bioaccumulation potential and worrying health risks (Fu et al., 2021). 11 organophosphates were detected in surface water and sediments from samplings yearly during 2013–2018 in Canadian Arctic (Sühring et al., 2020). In wildlife and fish, organophosphate metabolites was

found in tissues. Organophosphates are synthetic chemicals found in highest concentrations in indoor environments due to their usage as flame retardants and plasticizers (Zheng et al., 2021).

2. Organophosphate esters in consumer products

Organophosphate esters are commonly used as plasticizers and flame retardants, applied to a wide variety of consumer products and have ability to leach from these products (Doherty et al., 2019). Flame retardants containing products include certain cloth textiles (Zhu et al., 2020), construction materials, home furnishings, children's products (Hammel et al., 2020) and many other. As a flame retardant they are added in plastics, curtains and carpets, exposure to them is widespread. Vulnerablility of children are higher than adults to related health risks such as inflammation and allergies. Oxidative stress is thought to modulate childhood airway atopic dermatitis and inflammation development (Bamai et al., 2019). Children are at higher risk due to proximity to dust containing surfaces, more hand to mouth activity, and being in critical neurodevelopment period (Gibson et al., 2019).

In consumer products, organophosphates are also commonly used as plasticizers, and exposureto them is relatively high in most populations. Concerns are being endocrine-disrupting, neurotoxic, and interference with behavioral development (Doherty et al., 2019). As a type, isopropylated triarylphosphate isomers may negatively impact cognitive development (motor skills and language abilities). Increasing number of evidence suggests that exposure prenatally to organophosphates may negatively affect cognitive development

(Doherty et al., 2019). Studies report that organophosphates may disrupt sex steroid hormones homeostasis (Luo et al., 2020). These esters are also found in electronics, processed foods and building materials. Emerging studies propose that they are metabolism disrupting compounds (Luo et al., 2020).

Organophosphate esters are related to adverse pregnancy outcomes such as reduced live births and fecundity and increased preterm delivery. They may interfere with metabolism and growth via endocrine-disruption (Crawford et al., 2020). Organophosphate flame retardants are related with reduced fertilization. They may affect infant anthropometry and that some of them may also affect feeding behavior (Crawford et al., 2019). Breastfeeding can a significant organophosphate esters exposure source for infants. Daily intakes of tri-organophosphate and di-organophosphate esters via lactation may be up to 50 times higher than intake through diet and dusts (Zheng et al., 2021).

3. Organophosphate pesticides

Many chemicals in environment are identified as neurotoxicants in experimental and epidemiological studies. Organophosphate esters started to be replace neurotoxic polybrominated diphenyl ethers in 2004. But they also become an important public health aspect regarding their potential for child neurotoxicity (Percy et al., 2021).

Organophosphates are used in many herbicides and insecticides. Approximately 3 million poisonings (unintentional + suicidal) with 0,3 million fatalities are reported due to organophosphates each year

worldwide (Dodson et al., 2021). These neurotoxic pesticides containing organophosphate are widely used in agriculture, leading to exposure in human populations everywhere (Nkinsa et al., 2020). Organophosphate pesticides can be hazardous to human health if not applied with appropriate precautions (Munoz-Quezada et al., 2019). Despite, information related to children's exposure to such pesticides is rare, vulnerablility of children are higher than adults, it is important to reduce exposure to these chemicals and protect children health (Gonzalez-Alzaga et al., 2020).

Pesticides containing organophosphate esters cause acute toxicity via inhibiting acetylcholinesterase and neurodevelopmental effects observed at low exposure concentrations. Contamination of conventional crop products via agricultural spraying with organophosphate pesticides is an important route for the general population exposure (Thistle et al., 2020).

Exposure of children to organophosphate pesticides can increase oxidative stress which result with the chronic diseases (Sapbamrer et al., 2020). Evidences support that pesticide exposure impacts renal function and kidney diseases. Urinary dialkyl phosphate metabolites are found associated with kidney injury in children of chronic kidney disease (Jacobson et al., 2021).

Hair is a better material than urine to assess exposure to organophosphate pesticides. It is easier to collect, handle and store hair than urine for cumulative organophosphate pesticides exposure assessment (Hernandez et al., 2019).

Organophosphate pesticides can be transfered to fetus via amniotic fluid and placenta. Maternal ethylated organophosphate pesticides exposure at pregnancy may influence infant developmental performance (Suwannakul et al., 2021).

4. Individual pediatrics studies on organophosphates

The levels of oxidative stress biomarkers and of 14 organophosphate flame retardants metabolites were measured in urine of 7-year-old total 400 children in the study of Bamai et al., (2019). They determined that organophosphate flame retardants metabolites, 2-ethylhexyl phenyl phosphate, bis(2-butoxyethyl) phosphate, and diphenyl phosphate were associated with increased levels of oxidative stress biomarkers. Organophosphate flame retardants metabolite mixture was associated with increased hexanoyl-lysine and 4-hydroxynonenal levels.

Higher concentrations of "bis(1,3-dichloro-2-propyl phosphate)" were associated with higher scores on the "Externalizing Problems" and "Behavioral Symptoms Index" composites. Among "Behavioral Assessment System for Children" scales, "bis(1,3-dichloro-2-propyl phosphate)" was most strongly associated with attention problems, withdrawal, depression, aggression and hyperactivity. Also concentrations of "Diphenyl phosphate" were associated with "Externalizing Problems" and "Behavioral Symptoms Index" composites. As a result, greater maternal exposure to "triphenyl phosphate" and "tris(1,3-dichloro-2-propyl phosphate)" during pregnancy was associated in children with adverse behavioral development (Doherty et al., 2019).

Exposure to organophosphate esters individually or as mixture was associated to decrease in levels of sex steroid hormones (total testosterone, free androgen index, and estradiol) and increase in levels of sex hormone binding globulin in pubertal individuals or adolescents (Luo et al., 2020).

In their study in agricultural and urban communities, Sapbamrer et al., (2020) compared urinary organophosphate metabolites and oxidative stress in children. Detected total dialkylphosphate levels in children in studies agricultural community were significantly higher than studies urban community. Diethylphosphate levels in agricultural community children were negatively associated with distances from residence to farming fields and positively associated with children working in farms. Glutathione levels in agricultural community children were significantly lower than detected in urban community.

Gibson et al., (2019) measured organophosphate exposure in maternal and child urine and wristbands. Two of six flame retardant metabolites measured in urine was at higher levels in children than mothers. Exposure of children were found more than mothers to tbutyl-DPHP and bis(1,3-dichloro-2-propyl) phosphate.

A motor inhibition task was performed during functional magnetic resonance imaging for 95 children aged between 10–12 years. Activity in frontal regions was decreased when organophosphate pesticides metabolites level was increased. It was concluded that organophosphate ester pesticides can be associated with altered activity in brain regions related to inhibition (Binter et al., 2020).

In the study of Zhu et al., (2020), profiles and concentrations of 20 different organophosphates were measured in 160 different textile materiasls collected in the United States. Significantly higher concentrations of organophosphates were found in 23 different fabrics containing flame retardant containing, especially in materials manufactured in the US. Trace amounts of organophosphates were also detected in infant textile. Triphenyl phosphate was the predominant compound (40% of total concentrations) determined in these textiles. It was followed by cresyl diphenyl phosphate (34%) and tris(1-chloro-2-propyl) phosphate (18%).

In a study of Hammel et al., (2020), biomarkers of organophosphate ester exposure were detected frequently among infants. Tris(2-chloro-isopropyl) phosphate metabolite levels were significantly higher at 6 weeks than at 12 months of age. Infants who were currently receiving breast milk had higher levels of tris(2-chloro-isopropyl) phosphate metabolites. Breastfeeding and owning more children's products were associated with higher bis(1,3-dichloro-2-propyl) phosphate.

Exposure to pesticides is a major factor in the cause of dysfunction in the nervous system and neurodevelopment disorders in children at critical periods of great vulnerability. A standardized methodology is needed to enable the comparison of the results in several studies, and further research studies are needed to warrant firmer conclusions (Sapbamrer & Hongsibsong, 2019).

5. Conclusions

Organophosphate esters found in cloth textiles, home furnishings, curtains, carpets, construction materials, electronics, processed foods and children's products contain them as additives. They are widely sprayed to agricultural crops as plant protection chemicals (insecticides, fungicides).

Children are more vulnerable than adults due to proximity to dust, high level of hand to mouth activity and being at critical neurodevelopment period.

Associated health risks are allergies, inflammation, oxidative stress, neurotoxicity, endocrine-disrupting, behavioral development problems, adversely impacted fine motor skills and early language abilities; homeostasis of sex steroid hormones, reduced fecundity, reduced live births, reduced fertilization, increased preterm delivery, affected infant anthropometry, affected infant feeding behavior.

Organophosphate esters have become an important public health topic as evidence regarding their potential for early-life neurotoxicity is growing

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CHAPTER 5

BENIGN AND MALIGNANT NEUROGENIC TUMORS OF THE MEDIASTINUM IN CHILDREN

Dr. Altay BABACAN[1]

[1] Fethi Sekin Pediatrics Hospital, Hematology-Oncology Department, Elazığ, Turkey
Correspondence: altay.babacan@hacettepe.edu.tr

INTRODUCTION

Mediastinal tumors have a wide histopathological distribution because different tissues and organs are located in the mediastinum. They can occur at any age, such as childhood, adolescence, adolescence, and adulthood. Neurogenic tumors, one of the cancers located in the mediastinum, are caused by cells in the embryonic nerve cells. These tumors are usually rare in the posterior midbrain, paravertebral sulcus (90-95%), chest wall, or in the paraprenchyma. They are equally present in both paravertebrates. Nerve cancer constitutes 20% of cancers in adults and 34-58% in children (Bicakcioglu, et al .,2014; Reynolds and Shields, 2009). The incidence of neurogenic cancer is 5-10% in adults and 40-60% in childhood. The risk of cancer increases with age.

Mediastinal masses of children are heterogeneous asymptomatic or life-threatening congenital, infectious, neoplastic lesions with complex diagnostic and therapeutic predicaments. Some patients are asymptomatic but others cause sudden asphyxia. For these cases, close cooperation is required between pediatric surgeons, intensivists, anesthesiologists, oncologists and radiologists (Freud et al., 2002). Neurogenic tumors are generally grouped into four categories, according to the source nerve cells, each has malignant and benign variants (Table 1).

Table 1. Histological types of mediastinal neurogenic tumors

Origin	Benign	Malignant
Nerve sheath	Neurilemmoma Neurofibroma Melanotic Schwannoma	Malignant schwannoma
Autonomic (Sympathetic) ganglia	Ganglioneuroma	Ganglioneuroblastoma Neuroblastoma
Paraganglionic system	Pheochromocytoma Paraganglioma	Malignant pheochromocytoma Malignant paraganglioma
Peripheral neuroectoderm	Melanotic Progonoma	Askin tumor

2. Mediastinal neurogenic tumors

2.1. Neurogenic tumors originating from the nerve sheath

These are the most common mediastinal neurogenic tumors in adults. This benign tumor group; neurilemmoma (schwannoma), melanotic schwannoma, neurofibroma, cancer; cancer or neurological sarcoma. 98-99% of neural cancers in adults are benign. Non-toxic injuries occur in young and middle-aged people. It is more common in women than men. It usually occurs as a single injury. Neurofibromatosis (Von Recklinghausen) is seen in patients with more than one disease

(Reynolds et al, 2009; Kocatürk, 2011). These tumors are usually located in the costoverebral dorsal cavity. In rare cases, it can originate from the vagus and phrenic nerves. They can also develop from the brachial plexus and intercostal nerves (Kocatürk,2011). It is asymptomatic in 92-94%. In some cancers, pleural pain due to nerve compression, Horner's syndrome and hoarseness can be seen. There may be an internal spread of cancer. There are reports that 30-40% of the spread of the disease is at the stage of diagnosis (Reynolds et al, 2009).

Radiologically, it usually appears as a circular, well-circumscribed mass adjacent to the vertebrae. This can cause bone erosion or increase the distance between the vertebrae. Nerve tumors may accompany calcification. Cancer is more common, its shape is irregular, and bone damage and erosion are more common. Computed tomography can be used to evaluate the spread of cancer and its relationship to peripheral nervous tissue, vertebrae, and spinal canals. MRI and myelography are available for cancers that have spread to the spinal canal. MRI "Dumbell" is a guide in tumors. Angiography can be performed to show the Adamkiewicz artery in tumors localized between T8-L1 (Orki et al, 2012; Hasdıraz,2011).

2.1.1. Neurilemmoma (Schwannoma)

These are benign, encapsulated tumors arising from Schwann cells. It is usually found as a single lesion. These are gray-brown, glazed, hard sores. Cystic and calcified degeneration areas can be seen. It may contain Antoni-A or Antoni-B cells. It consists of Anthony-A type

coronary artery cells. Anthony-B-shaped cysts and hemorrhages are seen. Seeing these cells separately or together makes no clinical difference. Toxic degeneration of neuralgia is very rare. Changes in cancer were reported as 2%. The final treatment is surgical removal and recurrences are rare(Negri et al., 2013).

Plexiform schwannoma: It is a benign lesion characterized in patients with neurofibromatosis. It is characterized by multiple unrelated tumor nodules and schwannoma of neoplastic connective tissue. It is more common in type 1 neurofibromatosis. Cell schwannoma: Histologically it can be confused with cancer. It is a benign tumor in pseudocharmatic form but with low mitotic activity. It is frequently seen in the paravertebral area. These tumors rarely recur, but do not metastasize.

2.1.2. Neurofibroma

They originate from all elements of peripheral nerve cells (schwann cells, perineural tissue and endoneural fibrous tissue). It is heterogeneous and well surrounded. Macroscopically, they are grayish yellow, soft, round, non-encapsulated, benign tumors. Usually alone. Neurofibromatosis (von Recklinghausen's disease) accompanies 14-30% of patients with moderate neurofibroma. Worsening of the cancer is common in people with multiple neurofibromas and von Recklinghausen. Surgical removal is sufficient for treatment (Kesieme et al., 2013). In children, neurofibromas rarely occur before age of seven (Biehl et al. 2020).

Plexiform neurofibroma; It is a variation of neurofibroma, in the form of diffuse fusiform enlargement and/or multiple masses along the peripheral nerve trunk. It is associated with neurofibromatosis or a familial history of the disease. Lesions are usually seen outside the thorax. It can be seen in the vagus or phrenic nerve in those with thoracic involvement.

2.1.3. Malignant Schwannoma

Schwannomas are sporadic and isolated tumors of adults aged greater than 60 years and are rare in children (Pathmanaban, et al., 2017). It is the most common type of cancer with a poor prognosis. It constitutes 1-2% of moderate neurological cancers. Von Recklinghausen disease has been attributed to 4% of cases. The onset of age in people with this disease is in the second decade. Non-hereditary forms are associated with radiation. The latent period after exposure to radiation is defined as 15 years.

2.1.4. Melanotic Schwannoma

They are pigmented tumors arising from the nerve sheath. As a rule, pigmented tumors of the sympathetic ganglion are toxic, while tumors of the nerve sheath are benign. These tumors are found in large numbers in the spinal canal. Macroscopically, they are bluish-black in color. Microscopically, the pigmented spindle cells form masses and bundles, and pseudomatous calcification may be seen. Treatment is surgical removal. Surgical planning should be done in conjunction with

neurosurgery because of the high dilation of blood vessels. Their prognosis is good, local recurrence can be seen, but metastasis has not been reported.

2.2. Neurogenic Tumors Originating from Autonomic (Sympathetic) Ganglions

They are the most common mediastinal neurogenic tumors of childhood. This group includes ganglioneuroma, neuroblastoma, and ganglioneuroblastoma. The mean age of infected persons was 22 months. 25% are diagnosed as under one year old. 97% occur before the age of ten. They are formed by sympathetic ganglion cells and adrenal glands. Tumors that develop from immature nerve cells are called neuroblastoma, if associated with immature nodular cells, they are called ganglioneuroblastoma, and fully differentiated nodal cells are called ganglioneuromas. Spontaneous regression, ganglioneuroma and ganglioneuroblastoma differentiation can be seen in neuroblastoma.

2.2.1. Ganglioneuroma

It is a benign tumor originating from mature ganglion cells. It can often occur as a result of maturation of a neuroblastoma. It constitutes 42% of neurogenic cancers caused by sympathetic ganglia. Although it is more common in children and adolescents, it is also more common in young people. Ganglioneuromas generally have favorable histological and clinical features. Surgery is often performed due to clinical symptoms (Alexander et al., 2018).

They are smooth, hard-consistent, encapsulated masses. The cut surface is yellowish white and in the form of a leiomyoma. The cytoplasm of the cell is eosinophilic and the cell nucleus is clearly visible. They are usually found in the paravertebral sulcus and attach to the intercostal and sympathetic nerve tunnels. It may extend into the spinal canal, but this is rare.

Clinical patients admitted to hospitals may have no symptoms. A large mass in the middle of the back can cause coughing, shortness of breath, Horner's syndrome and chest pain. Serum VMA and HVA levels are normal in the laboratory. Diarrhea may occur due to the release of intestinal vasoactive polypeptide (VIP). The VIP version is a good guess (Kesieme et al., 2013).

Radiologically on direct graphy; It appears as a well-circumscribed, oval or lobulated solid mass in the paravertebral space. Calcification is present in 50% of them. Calcification, which is widely and widely evaluated on CT, is evaluated positively for benign lesions. CT scan shows a homogeneous or heterogeneous hypodense area. Spinal canal dilatation can be evaluated using MRI. Ganglioneuroma treatment is surgery. Local recurrence is rare.

A five-year-old girl, who applied to Cerrahpaşa Pediatric Surgery clinic with the complaint of cough, showed a well-circumscribed mass in the right hemithorax in her chest X-ray, and CT and MRI were performed. On MRI, it was seen that the mass was distributed from the T5-6 level to the nerve hole. The mass was completely excised by right lateral

thoracotomy. Histological examination revealed a ganglioneuroma. The patient is followed for 1.5 years without any problem (Fig. 1).

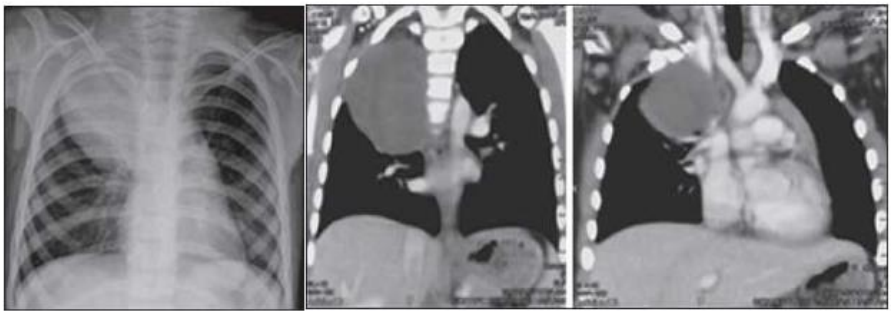

Fig. 1. Chest X-ray, and CT and MRI of a five-year-old girl patient with a mass in the right hemithorax

2.2.2. Neuroblastoma

It arises entirely from immature neural crest cells. It constitutes 10% of childhood cancers. More than half of all cases are under the age of two. The ratio of males to females is 1.2:1. It can develop anywhere in the sympathetic nervous tissue. It can occur in the cervical vertebrae. The tumor is located in the retroperitoneal region in 75%, in the middle of the back in 20%, and in the cervical and pelvic region in 5%.

Neuroblasts determine clinical status by following three pathways:

- ✓ They regress spontaneously.
- ✓ They show maturation from neuroblastoma to benign ganglioneuroma.

- ✓ As they progress, they become treatment-resistant malignant tumors (Başaklar et al., 2006).

The clinical complaint varies according to the location of the tumor, the presence of metastases, and the metabolic products of the tumor. Patients with moderate neuroblastoma often present with symptoms of cough, shortness of breath, and chest pain. Horner's syndrome can occur in the presence of cervical and upper extremities. It can metastasize to the orbital bone and cause proptosis or periorbital ecchymosis (panda eye). Dumbbell or hourglass tumors can compress the spinal canal, causing neurological symptoms. Symptoms associated with cancer metabolites may also occur. Hypertension is observed in 25% of cases due to the release of catecholamines. Redness of the face may be accompanied by excessive sweating and restlessness. Acute cerebral ataxia and nystagmus (dancing eye syndrome) caused by autoimmune mechanisms may be seen. The disease is usually accompanied by middle and lower extremity cancer, stage 1-2 and is a good prognostic sign (Başaklar et al., 2006; Su and Laberge, 2008).

Neuroblastoma may involve many body systems so, the radiologist must rely on multi-modality imaging (Hiorns and Owens, 2001). Neuroblastoma spreads locally, lymphatic, or hematogenously. Involvement of lymph nodes, liver, bone and bone marrow is common. Lung metastasis has been reported in 4% of cases. Distant metastases of mediastinal neuroblastomas are rare.

Amine Precursor Uptake and Decarboxylation (APUD) group tumors. In 85-92% of cases, catecholamine degradation products increased. It was determined that the VMA and HVA values in the urine of patients with undeveloped and undifferentiated cancer increased within 24 hours. The VMA/HVA ratio is predicted and it is reported to be good if it is above 1-1.5 (Topuzlu, 2006; Arapis et al., 2004).

Neuron-specific enolase (NSE) is an enzyme made by nerve cells and neuroblasts. A serum level of NSE greater than 100 ng/L supports the diagnosis of neuroblastoma. Increased serum LDH and ferritin levels are among the accompanying laboratory findings.

Direct X-rays show spot-like calcification in more than 50 percent of cases. Rib erosion and enlargement of the vertebral column may be seen. CT shows calcification in 80% of cases. MRI is a very effective way of demonstrating intrauterine proliferation. MIBG (metaiodobenzylguanidine) scintigraphy is useful in demonstrating soft tissue and bone metastases.

While the Evans and St. Jude staging system was used in neuroblastoma staging in previous years, the International Staging System for Neuroblastoma criteria were created in 1986 and updated in 1993. This systemic system monitors whether the tumor has been completely removed, crossed the midline, and is associated with the surrounding lymph nodes, posterior midbrain, retroperitoneal paraspinal node, adrenal medulla, and Zuc (Başaklar et al., 2006; Su and Laberge, 2008). Neuroblastoma is macroscopically a large, vascular, gray-purple mass

containing solid-cystic areas. It has a very fragile pseudocapsule that can bleed and rupture during surgery. Tumors are dead, especially in indistinguishable forms. The more mature the tumor, the larger the solid component. In the cancer microscope, the cells range from neuroblasts to small round cells that do not differentiate. Homer Wright pseudoroset formation is seen in 1/3 of them. Stroma-deficient neuroblastomas can be confused with other small round-shaped blue cell tumors (Ewing sarcoma, rhabdomyosarcoma, non-Hodgkin lymphoma, PNET). Electron microscopy and immunohistochemical studies are used to confirm the diagnosis. One of the most important factors determining the prognosis in neuroblastoma is the histology of the tumor. According to the criteria defined by Shimada, it was determined whether the disease had a good or bad prognosis. Shimada's criteria; Presence of Schwann cells with features such as stroma, mitosis/cariorex index (MCI) and cell differentiation. According to Shimada, in neuroblastomas, the extent of stromal fibrosis increases as the cells differentiate into nodal cells and the prognosis improves. Stroma-poor tumors contain indistinguishable neurons and have a high mitotic cariorex index. In the Shimada classification;

- ✓ Children younger than 18 months with low BMI regardless of the degree of differentiation,
- ✓ Tumors with rich stroma and well differentiated,
- ✓ Children aged 18 months to 5 years with well-differentiated, low BMI have a good prognosis.

- ✓ In the poor prognosis group;
- ✓ Those with undifferentiated histology and high MMI regardless of age,
- ✓ Undifferentiated histology, medium or high BMI, children aged 18 months to 5 years,
- ✓ All children over the age of five,
- ✓ Tumors with nodular structure are present.

Shimada also reported that N-myc amplification is also effective in prognosis. N-myc amplification of more than ten copies is associated with advanced disease and poor prognosis. Survival rates are 85% in those with favorable histology and 41% in unfavorable types (Başaklar et al., 2006).

Prognostic factors play an important role in the treatment of mediastinal neuroblastoma. According to this; Complete surgical resection should be performed in low-grade (stage 1-2) patients and in stage 4S patients with good histology. Regional lymph nodes should also be removed during excision. In case of spinal cord dilatation or penetration, neurosurgery should be planned and, if necessary, laminectomy should be performed. To avoid laminectomy, chemotherapy can be performed by taking a biopsy before surgery. Chemotherapy and surgery are combined in stage 3-4 cancer and stage 4 patients with poor histology.

Especially in the case of large chest neuroblastoma, chemotherapy or chemotherapy+radiation therapy is given first (Arapis et al., 2004).

In the X-ray of a patient with respiratory distress in our 25-day hospital, a mass that had spread to the nerve hole was detected in the posterior middle part of the right hemothorax. The mass was completely excised with the aid of a thoracotomy. Histopathological diagnosis is a neuroblastoma. Patients with suitable histology are followed for 10 months without any problems.

2.2.3. Ganglioneuroblastoma

It is a form between ganglioneuroma and neuroblastoma. It has a malignant character but has a better prognosis than neuroblastoma. Microscopically, it contains mature ganglion cells and neuroblasts. Its incidence in the thorax is equal to neuroblastoma. It is usually located in the paravertebral sulcus. 50% of them are asymptomatic and the diagnosis is made on incidental chest radiographs. Erosion of the ribs can be seen in 5-10% of cases. May contain point calcifications. Extension into the spinal canal is not as common as neuroblastoma. Elevated VMA and HVA levels can be seen in 12% of cases.

2.3. Neurogenic Tumors Originating from Paraganglionic system

2.3.1. Paraganglioma

They are very rare tumors in childhood. Paragangliomas can originate from sympathetic or parasympathetic ganglia. Parasympathetic

paragangliomas do not secrete catecholamines and are chromaffin negative. These are called chemodectomas. The active forms that synthesize catecholamines are called pheochromocytomas.

2.3.2. Pheochromocytoma

Pheochromocytoma tumors are rare neuroendocrine tumors and knowledge on conditions in children are lacking (Park et al, 2020). Management and outcome of pediatric pheochromocytoma is uncertain due to limited number of cases (Ciftci et al., 2001). Pheochromocytomas tumors (arise from adrenal medulla) and paraganglioma tumors (have extra-adrenal origins) are rare in children. Pheochromocytomas usually secrete catecholamines and paragangliomas either secrete catecholamines or are nonfunctional (Young, 2018.

2.3.3. Malignant pheochromocytoma

Based on the literature, average children age of pheochromocytoma is 11-12 years for time of diagnosis. Epidemiologic differences exist between the tumor manifestation in adults and children (Beltsevich et al., 2004). Combination chemotherapy is a good option for the treatment of malignant pheochromocytomas (Elder , 2003).

2.3.4. Malignant paraganglioma

Paragangliomas are rare tumors sourced from neural crest cells and their origins vary along the sympathetic nervous system. They are

mostly characterized by catecholamines secretion. If they are biochemically inactive, diagnosis is often problematic. Malignant paraganglioma is defined by the presence of this tumor at sites where chromaffin cells are usually not found or by local invasion of the primary tumor. Recurrence generally occurs within five years. Malignancy is linked to a SDHB mutation in general (de Paula Miranda, et al., 2015).

2.4. Neurogenic Tumors of Peripheral neuroectoderm Origin

2.4.1. Melanotic Progonoma

It is a pigmented neuroectodermal tumor seen in infants. It is rarely seen in the mediastinum, most often in the chin area. Local recurrence is seen in 15% of cases. Its treatment is surgical resection (Reynolds and Shields, 2009).

2.4.2. Askin Tumor

It is a malignant, small cell tumor that affects the thoracic and pulmonary areas and is seen in children and adolescents. It is located in the paravertebral region, on the posterior wall of the chest, and in the lungs. It is thought to originate from the intercostal nerves. It is more common in older children and adolescents and is three times more common in girls. Standard treatment is a broad cut. Radiation and chemotherapy can be used, especially after incomplete pruning. Local recurrences are common, the prognosis is poor, and the average survival time is about 8 months.

3. Surgical Principles in Mediastinal Neurogenic Tumors

Surgical resection is the first line of treatment for all mediastinal nerve tumors. In the case of neuronal carcinoma, it is possible to completely remove the tumor by thoracotomy or thoracoscopy. Chemotherapy or radiation therapy can be used in addition to surgery in nervous system cancers.

Surgical resection is curative in stage 1-2 neuroblastomas originating from the sympathetic ganglia. There are many publications reporting successful results with thoracoscopy in these cases. If the injury extends into the spinal canal and neurological symptoms occur, the spinal cord should be removed first. This may include laminectomy/laminotomy, radiation therapy, and chemotherapy. Tumors that are inward during surgery should be removed in a single session. First, the neurosurgery team should test the area up to the spinal canal (Fraga et al., 2012; Tekant et al., 1997).

The classical approach in the surgical treatment of mediastinal tumors is removal of the mass by thoracotomy. However, thoracoscopy has become more common in recent years, especially in benign lesions. Advantages of this method; short operative time, short hospital stay, low postoperative pain, low morbidity and mortality. Thoracoscopy is indicated for tumors larger than 6 cm, involving the spinal arteries, and tumors located in the middle. Thoracoscopy may also be used with a neurosurgery team for neuroblastomas that have spread to the spinal

canal. With the correct surgical procedure and complete removal of the injury, recurrences are very rare (Fraga et al., 2012; Tekant et al., 1997).

4. Conclusions

In general, primary mediastinal mesenchymal tumors include rare tumors of the mediastinum. These cases are usually asymptomatic and nonspecific symptoms occur in the absence of symptoms. However, as a result of compression of the surrounding tissues and organs, a picture similar to superior vena cava syndrome, Horner's syndrome, dyspnea, dysphagia or arrhythmias can be seen. In this case, the presence of weight loss is an important information showing that the mass that may have complained may be cancer. Moderate enlargement is usually seen on anterior and posterior chest radiographs, leading to moderate suspicion of a mass. A CT scan of the chest will provide the necessary information for diagnosis and help identify the mass and its characteristics. It will provide important information such as whether the mass is cystic or solid, the size of the adipose tissue, whether it is calcified or dead, whether it penetrates the surrounding tissues and organs, and the displacement of interstitial structures. Chest magnetic resonance imaging will provide useful information in cases of suspected attacks; MR angiography will give surgeons information about the mass of blood vessels in the suspicious mass. Embolization of the high-vessel cancer feeding vessel before surgery will ensure safety and save the patient's life. Complete surgical resection is usually recommended for the treatment of mediastinal mesenchymal cancer, and there is insufficient information about chemotherapy and radiation

therapy for most cancers. Use of CPB is recommended when necessary for invasive cancer to perform a complete surgical incision. A complete surgical resection will have the advantage of getting rid of more than one cancer. Depending on the type of histopathology of the tumor, the case should be monitored regularly for local relapses and relapses, and potential relapses should be detected and treated early. However, if these points are taken into consideration, the survival time of the cases can be long and their prognosis can be good.Author Contributions: N.T.; Problem identification and Construction of insilico pipeline, N.T.; Data retrieval, N.T.: Data analysis and data interpretation, N.T.; A.S.; Manuscript writing— N.T.; A.S.; writing—review and editing, A.S.; funding acquisition N.T.; All authors have read and agreed to publish the version of manuscript.

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CHAPTER 6

THROMBOCYTOPENIA IN CHILDREN

Dr. Altay BABACAN[1]

[1] Fethi Sekin Pediatrics Hospital, Hematology-Oncology Department, Elazığ, Turkey Correspondence: altay.babacan@hacettepe.edu.tr

INTRODUCTION

"Immune Thrombocytopenia" (ITP), (old name "Im-mune-Thrombocytopenic-Purpura") is normal or increased number of megakaryocytes in the bone marrow, increased antibody and T cell mediated platelet damage, presence of thrombocytopenia with normal erythrocyte and leukocyte values, splenomegaly and the absence of other secondary causes of thrombocytopenia, is a common, acquired autoimmune disease.

Immune thrombocytopenia is usually diagnosed between the ages of 1-9, and it is most common in children aged 2-5 years in this age group. Its incidence is 4-5,3 per 100,000. According to the duration of ITP, new diagnosis is divided into three as per-sistent and chronic ITP. New diagnosed ITP covers the first 3 months after diagnosis. ITP is Persistent when cases do not go into remission spontaneously or cannot remain in remission when treatment is not given, covering 3-12 months after diagnosis. ITP is defined as Chronic if lasting 12 months or longer (Rodeghiero et al., 2009).

Immune Thrombocytopenia

Purpura in Latin word of "purple" and refers to reddish purplish lesions caused by bleeding under the skin. German Poet and Doctor Paul Gottlieb Werlhof (1699-1767) gave the classic definition of ITP in 1735. He described a disease called "morbus maculosus hemorragicus" in a girl aged 16 years old with cutaneous and mucosal bleeding, and

the picture was later referred to as Werlhof's Disease (Stasi, 2011; Freedman , 2003).

Later, Werlhof's Disease was defined as "simple purpura (purpura simplex)". Many important developments continued until the end of the 19th century, including the discovery of platelets and megakaryocytes. Paul Kaznelson, a medical student in Prague, suggested in 1916 that the spleen is the organ where platelet destruction takes place, and persuaded his teacher, Professor Doctor Schloffer, to perform the first sple-nectomy in ITP on a 36-year-old female patient who met the definition of chronic ITP. After splenectomy, it was observed that there was a significant increase in thrombo-cyte counts in the patient. The immune aspect of ITP was first demonstrated by Wil-liam J. Harrington in 1951, when blood obtained from ITP patients was given to nor-mal volunteers, with a significant decrease in platelet counts. In 1951, Evans defined plasma factor as an antiplatelet antibody. Also in these years, Wintrobe was the first to use steroids in the treatment of ITP. Imbach successfully applied intravenous immu-noglobulin (IVIG) in the treatment of ITP in 1981. Subsequently, Salama et al. reported the application of anti-D for ITP treatment. At the end of the 20th century, rituximab, a monoclonal antibody, started to be used especially in the treatment of chronic and re-fractory ITP patients. Thrombopoietin (TPO) is used especially in patients with severe refractory chronic ITP [2, 3].

As the options for ITP treatment continue to expand, patient identification to treat rituximab is becoming more complex. Guidelines

for rituximab treatment for ITP differ in adults than children and rituximab treat decision may vary according to age (Harris et al., 2020).(

For pediatric chronic immune thrombocytopenic purpura, indications and timing of splenectomy are controversial due to high levels of spontaneous remission rates and concerns on overwhelming postsplenectomy infections (Gwilliam et al., 2012).

ITP is a hematological disorder that affects patients of all ages, genders and races, and is the most common blood disease. The disease etiology is still unknown. Although initially defined as 'idiopathic thrombocytopenic purpura', the disease was defined as 'Immune Thrombocytopenia' by the ITP International Working Group and the abbre-viation ITP was not changed. While this nomenclature reflects the immune basis in the pathogenesis of ITP, it emphasizes that not all ITP patients will have a similar course of purpura or bleeding symptoms (Rodeghiero et al., 2009).

It is generally accepted that immune thrombocytopenia of children differ from adults for clinical course; for bleeding risk, rate of spontaneous remission and treat-ment need (Kuehne, and Schifferli, 2016).

International Working Group has designed a classification standard for the dis-ease. According to this draft, primary ITP is defined as isolated thrombocytopenia (platelet count <100X109/L) in the absence of other cause or disease to cause thrombo-cytopenia. Secondary ITP includes

other non-primary types of thrombocytopenia due to infections such as hepatitis C infection, systemic lupus erythematosus or lymphoproliferative diseases.

An major mechanism for thrombocytopenia in primary ITP is “autoantibody sen-sitized coated platelets” phagocytosis through “Fc gamma receptors” on phagocytic cells (Zakaria et al., 2021).

Classification of Immune Thrombocytopenia

Immune thrombocytopenia is classified according to its etiology, disease course and age of onset. According to the course of the disease, ITP is examined in three categories as newly diagnosed, persistent and chronic (Rodeghiero et al., 2009; ITP). ITP that affects young children is usually newly diagnosed and self-resolving, with the primary forms being most com-mon at this age. At adolescents, ITP shows a increased rate of chronicity and percent-age of secondary ITP, which is an intermediate type between childhood and adult forms (Lowe and Buchanan , , 2002).

The etiological classification divides ITP into two categories, primary ITP and secondary ITP. The primary form of ITP, classically defined as "idiopathic", is fre-quently seen in childhood and is triggered by nonspecific viral infections (upper res-piratory or gastrointestinal infections). In some cases, Epstein-Barr virus, cytomegalo-virus, parvovirus, rubella, mumps and varicella have been identified as triggers of ITP (Smalisz et al., 2015).

The etiology of secondary ITP is complex as specific infections, drugs, vaccines, and immunological abnormalities, including immunodeficiencies, may play a role in its pathogenesis. Infectious agents such as HIV, HCV, Helicobacter pylori, and Dengue virus can trigger secondary ITP, usually with a chronic course, through different mechanisms such as molecular mimicry, modulation of immune system activity, or suppression of bone marrow production (Shah, 2013; Pacifico et al, 2014; Abdollahi et al., 2013).

Medicines and vaccines

Medications and vaccines can cause secondary ITP: most antibiotics, nonsteroidal anti-inflammatory drugs, and antivirals result in recurrent and unexplained episodes of thrombocytopenia. This situation usually shows complete recovery after discontin-uation of the drug (Reese et al., 2013).

ITP might be in front of silent viral infections. Also antiviral drugs and vi-ral-vaccines may trigger immune thrombocytopenia and play a major role in its path-ogenesis. The seasonal nature of children ITP suggests that viral infections may be ini-tiating immune responses which increase predisposition and the occurrence of im-mune thrombocytopenia (Elalfy and Nugent, 2016).

Studies have reported an increased risk of ITP with measles-rubella-mumps, hep-atitis A, varicella, tetanus-diphtheria-pertussis vaccines in young children. This situa-tion observed in vaccines can be explained by the molecular mimicry theory and/or by exposure to specific

antigens in susceptible individuals, with the initiation of immune stimulation and the disappearance of tolerance to platelets (Cecinati et al. 2013).

Iminine insufficiency

Immune thrombocytopenia may be a manifestation of immune deficiency like common selective IgA deficiency, Di George Syndrome and variable immunodeficiency (CVID). Decreased platelet count in humoral immune defects may occur years before hypogammaglobulinemia (Patuzzo et al., 2016).

Autoimmune diseases

Systemic autoimmune diseases such as systemic lupus erythematosus (SLE), Sjögren's syndrome and antiphospholipid syndrome are associated with the development of ITP. Isolated thrombocytopenia may be the initial manifestation of SLE until years before diagnosis (Liu et al, 2016). In addition, it has been reported that there is a relationship between ITP and autoimmune clinical and subclinical thyroid diseases (Hashimoto and Basedow Graves Disease) (Marta and Campos, 2015). Chronic ITP might coexist with rheumatologic diseases, thyroid diseases and immunodeficiencies due to probable immunity dysregulation (Güçer et al. 2018). More-over, many lymphoproliferative disorders can cause secondary ITP. The most common disease in this category is autoimmune lymphoproliferative syndrome, which is mostly seen in children under the age of 3 (Li et al.,

2016). Lymphatic malignancies, especially Non Hodgkin lymphoma, may be a cause of immune thrombocytopenia (Stern et al. 2007).

Immune thrombocytopenias in children

Newly diagnosed ITP is a common diseases of childhood which does not require de-tailed laboratory diagnosis. Peripheral smear with examination of history and physical conditions are critical for excluding secondary reasons of thrombocytopenia. A few guidelines was published to help physicians for the ITP management. However, treatment decision can be hard. Strategy for management should not be concentrated on the platelet count. Agents like corticosteroids, immunoglobulin and anti-D immuno-globulin for treating don't seem significantly effective on the natural history of the acute ITP disease. Most of the children diagnosed ITP do not require therapy and have a spontaneous solution of this disease. Children may develop chronic ITP which is not life-threatening but reducing quality of life. Therapies of rituximab and splenectomy for chronic ITP may have adverse effects. Newer promising agents for the treatment of chronic ITP are thrombopoietin receptor agonists, but their cost are currently high for many patients in low or middle income countries (Singh et al., 2020).

Causes of immune thrombocytopenia; This includes the destruction of plates in the re-ticuloendothelial system, mainly in the spleen. Immunosuppression by platelet anti-bodies is mediated by an immune complex that directly targets the antigen on the platelet or binds to the Fc receptor on the platelet (Marta and Campos, 2015). Thrombopoietin receptor ago-nist drug romiplostim can be effective for the treatment of

symptomatic children with chronic or persistent immune thrombocytopenia (Tarantino et al., 2016) and is approved globally for use in the European Union for children with ITP (Tarantino et al.,2018).

The thrombopoietin receptor agonist eltrombopag was shown as safe and effective for adults with chronic immune thrombocytopenia (Grainger et al., 2015) and is approved for oral treat-ment of adults with chronic immune thrombocytopenia (Bussel et al., 2015).

Platelet specific antigens are complexes such as GPIIb-IIIa or GPIb-IX-V in the glyco-protein structure found only in the platelet membrane. Differences in the genetic makeup of glycoproteins in platelet membranes reveal platelet alloantigens.

HPA (Human Platelet Alloantigen) numbering system has started to be used, similar to the HLA system, in order to avoid confusion in the naming of the increasing number of platelet alloantigens. Platelet alloantigen is classified according to the "Human Platelet Antigen (HPA)" system. 14 serologically defined alloantigens (HPA -1, -2, -3, -4, -5, -6, -15) were grouped. Platelet-specific alloantigens are located on platelet glycoproteins. HPA-1a causing neonatal alloimmune (isoimmune) thrombocytopenia (NATP) and many clinically important alloantigens are localized in GPIIb-IIIa. Platelet non-specific antigens are HLA class I and AKI group antigens found on leukocytes and other cell types and platelets (Reese et al. 2013).

Regardless of which antigen group is produced, clinical syndromes like post-transfusion purpura, autoimmune thrombocytopenia, neonatal

alloimmune thrombocytopenia and platelet resistance are associated with platelet destruction (Marta ande Campos , 2015).

Foetal and Neonatal Alloimmune Thrombocytopenia is a genetic disorder, rare and generally not diagnosed until the born of a child. Its rarity makes it hard to diagnose due to confusion of symptoms with normal birth trauma (Schofield et al., 2019).

Autoantibodies have been reported mostly against GPIIb-IIIa and less against GPIb or GPIX in immune thrombocytopenic purpura. Bone resorption resistance is alloan-tidenes against HLA class I antibodies, particularly HLA-A and HLA-B, which are well expressed on the plate. These antibodies develop in people who have had more than one blood transfusion and in women who have had more than one birth. In drug-containing thrombocytopenia (Table 3), autoantibodies are usually rare against IIIIb-IIIa and, unlike ITP, against GPIb or GPIX (Reese et al. 2013).

Immune (Idiopathic) ITP (thrombocytopenic purpura) in children

Immune (or idiopathic) thrombocytopenic purpura (ITP) is manifested by sudden bruising, petechiae and purpura in a previously healthy child, there is no pathological finding except bleeding findings in physical examination, blood elements other than thrombocytopenia are normal, other thrombocytopenia It is a disease that usually starts 1-4 weeks after a viral infection or vaccination and is known to be completely healed by 80% spontaneously (Patuzzo et al. ,2016).

ITP disease has heterogenous origin characterized by low platelet counts and bleeding. It has three phases: 1) new diagnosed (≤ 3 months after diagnosis), 2) persistent (> 3–12 months after diagnosis), 3) chronic (> 12 months after diagnosis). Most of the children have short-lived ITP disease and require no treatment. Short courses of steroids are recommended for children with new diagnosed ITP with increased bleeding symp-toms. Thrombopoietin receptor agonists are recommended for children who do not re-spond to first-line treatment or became steroid dependent, due to efficacy and safety profiles (Grainger et al., 2021).

Platelet and megakaryocyte membrane glycoprotein autoantibodies play a role in the pathogenesis of ITP. These antibodies increase platelet phagocytosis destruction, but affect platelet secretion from megakaryocytes in the bone marrow. It is not entirely clear what stimulates the production of autoantibodies.

ITP is a very common condition for pediatric hematologists and first-line therapy in-cludes: 1) no drug therapy but observation of patients, 2) corticosteroids and intrave-nous immune globulin. A few patients are resistant to first-line approaches. Options for second-line treatment are: 1) immunosuppressive agents 2) thrombopoietin recep-tor agonists. Eltrombopag and Romiplostin are thrombopoietin receptor agonists li-censed for clinical use (Giordano et al., 2018).

Younger ITPs, unlike adults, do not have gender differences, start suddenly, are mildly contagious, and less than 20% are chronic. For ITPs with the usual clinical manifesta-tions in children, the disease is

benign and usually resolves spontaneously without any treatment. There is consensus that bone marrow transplantation is not necessary un-less the patient is observed and treated with immune globulin and steroids alone. The aim of drug therapy is to prevent life-threatening bleeding (frequency of intracranial bleeding 0.1-0.5%) (Patuzzo et al., 2016).

Paediatric ITP is generally a benign condition resulting with spontaneous remission in 6–12 months for many children (Neunert and Grace, 2015).

As drug therapy; Corticosteroids, which inhibit phagocytosis and production of anti-body coated platelets and increase platelet production, can be used in various dosages and models. It is clear that no treatment can affect the course or chronic course of the disease. Steroids and IVIG can be used in emergencies, sometimes to treat chronic pa-tients who are at risk of bleeding and do not respond to medical treatment. (Stern et al., 2007).

Corticosteroids are the globally accepted first-line therapy for severe or moderate ITP (Ragab et al.,2015).

Management of new diagnosed ITP in children with requires careful observations or treatment with corticosteroids or intravenous immunoglobulin (Heitink-Polle et al., 2016).

Prednisone is generally a first-line therapeutic agent for ITP at children. But prolonged prednisone usage was associated with some side effects (Ma et al., 2020).

Cyclosporin A was found effective at some of children with chronic ITP. It can reduce chronic steroid therapy and/or splenectomy requirement (Liu et al., 2016).

In the absence of treatment, the choice of treatment requires the experience of a physi-cian. The aim is not to treat the platelet count, but to determine the risk of bleeding and to treat the patient. Patients with large, active platelet-producing ITP on peripheral smears should be aware that bleeding is not possible without the use of drugs that im-pair platelet function, are not injured, or have vascular abnormalities.

Complete removal of spleen, as the main site of platelet degeneration and antibody production in chronic pediatric ITP, is a treatment that provides 50-70% cure. For chronic hemorrhagic ITP; Anti-D immunoglobulin and anti-CD-20 monoclonal anti-bodies (Rituximab) are possible treatment options.

Immune thrombocytopenic purpura (ITP) is a common hemorrhagic problem in chil-dren generally caused by an acute self-limiting event. 30% of these children develop chronic ITP. Identifying underlying reasons in ITP is a significant challenge. Inherited thrombocytopenia is rare, underdiagnosed and included among chronic platelet dis-orders. Next generation sequencing can be effective for the discovery of potential associated mutations in children with chronic ITP (Mohamed et al., 2020). Diagnosis should focus on ITP, collagen vascular disease such as Hodgkin's, autoim-mune lymphoproliferative syndrome (ALPS), SLE and leukemia, and pre-treatment differential diagnosis especially in the chronic form.

CONCLUSION

Platelets; They are very important blood elements in the first phase of hemostasis, where the platelet plate develops. The number of these cells is insufficient or function-ally insufficient; It causes bleeding involving the skin and mucous membranes, espe-cially petechiae, purpura ecchymosis, epistaxis, hematuria, menorrhagia, gastrointes-tinal and peripheral bleeding. Intracranial bleeding is very rare. General information about immune thrombocytopenic purpura and heparin-induced thrombocytope-nia/thrombosis will be given by considering the conditions that cause platelet defi-ciency in infants and young children separately. Causes of immune thrombocytopenia; This includes the destruction of platelets in the reticuloendothelial system, mainly in the spleen, due to antibodies against membrane antigens such as autoantibodies, al-loanthodes or drug-induced antibodies. Immune damage due to platelet antibodies is mediated by an immune complex that directly targets the antigen on the platelet or binds to the Fc receptor on the platelet.

Platelet antigens are divided into two classes. Platelet-specific antigens and platelet non-specific antigens. Platelet-specific antigens; They are complexes such as GPIIb-IIIa or GPIb-IX-V in the glycoprotein structure that is only on the platelet membrane. Ge-netic structural differences in glycoproteins in the platelet membrane reveal platelet alloantigens.

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CHAPTER 7

CANCER NURSING

Dr. Emral GÜLÇEK[1]

[1] Siirt University, Faculty of Health Sciences, Department of Nursing, Siirt, Turkey
Corresponding author: canan_gulcek@hotmail.com

1. Introduction

With almost 20 million new cases and 10 million deaths worldwide, cancer is the 2nd cause of death in 2020. Care of cancer patients is complex and nurse demanding. Fatigue is common distressing symptom for cancer patients, families and health professionals. Care dependency is a distressing experience by cancer patients. Diseases has physical, cognitive, emotional and behavioural effects on patients which are produced by chemotherapy, radiotherapy and surgery. High-quality nursing can improve the negative emotions, quality of life and nursing satisfaction, and reduce adverse reactions of patients. Palliative care, supportive care, good communication, complementary therapies for relaxation, stress management, nutrition advices should be provided appropriately.

Here in this review, some actual findings related to cancer nursing published in the last decade in international articles are given.

Cancer is the 2nd cause of death worldwide (Lavdaniti, 2019). Worldwide 19,3 million new cases of cancer and almost 10,0 million deaths were estimated from cancer in 2020. The most diagnosed cancers were female breast cancer (2,3 million cases), lung (2,2 million cases) and prostate cancers (1,4 million cases) globally. Major common causes of cancer death were lung (1,8 million deaths), liver (0,8 million deaths) and stomach cancers (0,7 million deaths) (Ferlay et al., 2021).

Breast cancer, as most common malignancy in women, is accounting for 23% of all cancers in women globally (Nottegar et al., 2016). Carcinoma of the cervix is the 2nd most common cancer in women

worldwide (Shah et al., 2012). In men, prostate cancer is the most common malignancy (Roehrborn & Black, 2011). The European Parliamentary Group on Breast Cancer and the European Society of Breast Cancer Specialists state that there is a need for EU agreed guidelines on breast care nursing and training. The curriculum was developed using a variety of sources by experts. Definitions for breast care nurse roles and activities and levels of practice are provided (Eicher et al., 2012).

The care of patients suffering from cancer and especially those facing the death is complex and demanding for nurses (Charalambous & Kaite, 2013). Fatigue is a multidimensional symptom in cancer patients which occurs both as a result of the cancer itself and as an adverse effect of treatment (Lavdaniti, 2019). Fatigue is a common and distressing symptom for cancer patients, their families, carers and health professionals. It includes physical, emotional, cognitive and behavioural components. It can be unrelenting, disrupts daily life, fosters helplessness and may culminate in despair (Kirshbaum, 2010). Depression is one of the most common psychological reactions of patients during diagnosis and treatment. Nursing self-care educational intervention can be used as an effective and cost-effective adjunctive therapy along with common treatments to reduce depression (Bouya et al., 2021).

To combat cancer, individuals receive either curative or palliative treatments which produce undesired symptoms. These symptoms often cause significant distress. Alterations in the normal flora of the gut may

also influence cancer symptoms (Kelly et al., 2016). Nursing interventions achieved significant physical and psychological effects on the lives of patients with cancer. Multidimensional nature of interventions by combining different elements reinforces the effect (Tuominen et al., 2019). Nursing intervention has also a positive effect on hope in cancer patients (Li et al., 2018).

2. Chemotherapy

Cancer chemotherapy is a potentially hazardous treatment. To enhance the safety of chemotherapy administration, ASCO and the Oncology Nursing Society (ONS) were developed standards through a structured, multidisciplinary, and consensus-driven process with expert input, literature review, and public comment. The final 31 standards addressed eight specific domains: staffing, chemotherapy planning, general chemotherapy practice, chemotherapy orders, drug preparation, patient consent and education, chemotherapy administration, and monitoring and assessment (Weingart et al., 2012).

Fatigue is a well known side-effect of chemotherapy and is commonly reported as the most distressing symptom. Its intensity increases as cycles of chemotherapy progress. Onset, duration and level of fatigue varies and depends on chemotherapy drugs types and therapy schedule. A thorough assessment of the symptom before chemotherapy and during it is required. Management includes therapy of etiologic factors, pharmacologic and non-pharmacologic interventions. Managing fatigue requires a coordinated effort by all members of the health team. Nurses should provide patients and their families with lifestyle

education and guidance programs on the benefits of pharmacological and non-pharmacological interventions to effectively manage fatigue in order to enhance survival and quality of life (Lavdaniti, 2019).

Symptoms such as anorexia, changes in taste, nausea - vomiting, diarrhea, stomatitis and constipation are common side effects of chemotherapy which may result with inadequate food intake and malnutrition. Many appropriate nursing interventions exist to alleviate these symptoms. Nurses plays important roles for patient care who have feeding problems during chemotherapy. Nutritional interventions are individualized and should be started immediately and incorporated into the care plan in order to be successful. Fort his aim, patients should be assessed for nutritional problems and weight loss regularly before and after starting treatment (Lavdaniti, 2014). Anemia can be one of the most prevalent causes of fatigue in cancer patients. Implementation of a nursing care program for cancer patients receiving iron supplementation affects iron-related blood parameters and fatigue positively among these patients (Barahoui et al., 2020).

In ambulatory cancer chemotherapy, it is important to select outcomes that nurses have most impact upon. Patient experience, nausea, vomiting, mucositis and safe medication administration were outcome areas most likely to yield sensitive measures of nursing service quality in ambulatory cancer chemotherapy (Griffiths et al., 2012).

For breast cancer patients, level of uncertainty and anxiety may increase when women experience unexpected side effects during chemotherapy. Nursing instruction can decrease uncertainty and elevate self-care

levels. Nurses may provide structured nursing instructions based on evidence-based guidelines to breast cancer women undergoing initial chemotherapy in order to promote self-care level and patient degree of control over their disease and treatment. This intervention may ameliorate patient and family uncertainties with regard to disease and chemotherapy complexity (Lien et al., 2010).

3. Radiotherapy

During radiotherapy, it is common for lung cancer patients to experience pain while swallowing of food and drink (odynophagia). In a study of Olling et al., (2018), observations from nursing practice was used to generate predictive models for odynophagia. Overall predictive performance was good. This predictive model for pain medication for odynophagia prior to radiotherapy was found supportive for radiotherapy technologists nurses in directing nursing interventions for patients at risk.

Evidence-based nursing can positively influence the negative emotional state of breast cancer patients after radiotherapy. At the same time, it is helpful in reducing the degree of lymph node edema on the affected side of the upper limb, thereby improving the function of the shoulder joint (Wang et al., 2020).

Whole course high-quality nursing can improve the negative emotions, quality of life and nursing satisfaction, and reduce adverse reactions of patients with liver cancer during radiotherapy (Ling et al., 2019).

Synthesizing the best available evidence on the effectiveness of nursing interventions in radiotherapy patient care is important. Most interventions focus on skin care, oral care, nausea and vomiting and nursing consultation. The use of Calendula officinalis and thyme honey were considered effective for preventing and treating radiodermatitis and mucositis (Abreu et al., 2021).

Rehabilitation nursing intervention can ameliorate dysphagia, improve the quality of life, and reduce the incidence of complications for patients with esophageal cancer undergoing radiotherapy (Zeng et al., 2021).

Integrated medical and nursing intervention can obviously relieve the unhealthy emotion and improve the nutritional status, quality of life and self-efficacy for patients with esophageal cancer undergoing radiotherapy (Wang et al., 2021). Shared decision-making has the potential to increase quality of care. Patients undergoing routine pelvic radiotherapy care perceive decision-making as being shared between patient and healthcare professionals. Healthcare professionals may need to pay extra attention to patients who may perceive that they share decision-making to a low extent (Efverman & Axelsson, 2021).

4. Care

Increasing burden of cancer in the world and socio-demographic trends imply that more cancer patients will face high levels of dependency. Care dependency is often is a distressing experience by cancer patients. They are concerned about becoming a burden to others. Dependence appears as an experience with strong relational connotations, which

enable patients to see differently their life, themselves, the world and others. Deeper insight into the meaning patients attach to care dependency can enable nurses to better meet the patient's needs, e.g. by improving caring relationships with patients (Piredda et al., 2016).

Palliative care for children and adolescents with cancer includes interventions that focus on the relief of suffering, optimization of function, and improvement of quality of life at any and all stages of disease. This care is most effectively provided by a multidisciplinary team. Nurses apply an integral role in team by identifying symptoms, providing care coordination and clear communication. Palliative care should be administered concurrently with curative therapy beginning at diagnosis and assuming a more significant role at end of life. This treatment approach have benefits of longer survival. Secondly, realistic and objective goals of care must be developed. A clear understanding of the prognosis by the patient, family, and all members of the medical team is required to develop these goals. The pediatric oncology nurse is pivotal in developing these goals. Third, effective therapies must be provided to prevent and relieve the symptoms of suffering which can only be accomplished with accurate and repeated assessments. The pediatric oncology nurse is vital in providing these assessments and must possess a working knowledge of the most common symptoms associated with suffering. With a basic understanding of these palliative care principles and competency in the core skills required for this care, the pediatric oncology nurse will optimize quality of life for children and adolescents with cancer (Docherty et al., 2012).

Cancer cachexia is a complex syndrome. It is involuntary weight loss partially due to muscle atrophy and is accompanied by functional decline. International expert consensus recommends nutritional support and counselling as a multimodal therapy for this syndrome. Poor nutritional intake can help for progression of the syndrome. There is potential for nurses to play an important role. However, nursing role's boundaries and the outcomes of nurse-delivered nutritional care in cancer cachexia are both uncertain and should be investigated (Hopkinson et al., 2015).

5. Complementary therapies

Oncology nurses are in the core of fight with increasing burden of cancer. Their contribution is required due to scale and diversity of care roles and responsibilities in its care. People-centred care and good communication are important components of cancer nursing care. Supportive care is in the central in oncology nursing which enables people to self-manage if possible. Globally, oncology nurses make a great positive difference to every country's cancer strategy (Young et al., 2020).

Pain management is suboptimal in nursing homes (Hunnicutt et al., 2017). Many complementary therapies and practical interventions may be helpful such as acupuncture, acupressure, relaxation, stress management, energy conservation measures, preparatory information, anticipatory guidance and attention-restoring activities (Kirshbaum, 2010).

Sexual health is the integrity of somatic, intellectual, mental, emotional and social aspects of any individual. The cancer causes higher rates of sexuality related problems than other chronic diseases. Both the cancer diagnosis and the methods of treatment such as organ excision, radiotherapy, chemotherapy, the usage of hormones and cytostatic negatively affect the sexuality (Oskay et al., 2011). In their study, Olsson et al., (2012) determined that cancer patients' need of talks about and support regarding sexuality was low during cares. But nurses conceived that they should talk about sexuality with the patients, but due to own attitudes, knowledge and skills, as well as conditions in the ward environment they usually did not. About what, when, how and by whom, cancer patients and their partners want information and supportive care related to sexuality need to be clarified.

Breast cancer survivors commonly report deficits in attention and memory, cognitive functions crucial for daily optimal functioning. Chemotherapy and endocrine therapy contribute to attention and memory deficits. Potential interventions for attention and memory deficits in breast cancer survivors are promising. These include cognitive remediation therapies aimed at training for specific areas of deficit, cognitive behavioral therapies aimed at developing compensatory strategies for areas of deficit, complementary therapies, and pharmacologic therapies (Frank et al., 2014).

Cancer survivors need to know about nutrition and other lifestyle behaviour changes to help them recover and potentially reduce the risk of the same cancer recurring or a new cancer developing. Nurses should

be able to provide appropriate and more consistent advice on nutritional issues, physical activity and weight management. High-quality nutrition education and training is required for nurses working across both the acute and primary care sectors. This is required to effectively monitor and advise patients and to know when, where and from whom they can access more specialist help. Interprofessional collaborative working across multi-centre settings is key to provide the best effective care and support for cancer survivors (Murphy & Girot, 2013).

Pediatric cancer diagnoses affect the entire family (parents, well siblings, the ill child and others). There is a need for "evidence-based" practice nursing studies of interventions focused on parent education, support, assistance and increasing family and well sibling knowledge on the child's illness (Williams et al., 2014).

Holistic nursing care requires attention to the spiritual dimension. This is particularly important when caring for patients with cancer. Cancer patients in spiritual distress are in a state of suffering related to lack of meaning in life. Sensitive diagnosis tools and language are required for nurses to make accurate judgments in situations of spiritual distress (Caldeira et al., 2017).

6. Conclusions

Nursing role and nurse-delivered nutritional care in cancer cachexia are uncertain and should be investigated. Holistic nursing care in team environments to apply diversified complementary therapies to reduce stress, pain and other side effects of the diseases is in the core of cancer patients care.

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CHAPTER 8

HYPERTENSION NURSING

Dr. Emral GÜLÇEK[1]

[1] Siirt University, Faculty of Health Sciences, Department of Nursing, Siirt, Turkey
Corresponding author: canan_gulcek@hotmail.com

1. Introduction

Hypertension is the major risk factor for mortality in the world. Projection models indicate 1,2 billion hypertensive patients will be in developing countries in 2025. Hypertension requires continuous long-term care to delay or prevent associated complication developments. Nurse-led hypertension management is effective and feasible to improve the outcomes of patients with uncontrolled blood pressure. Successful implementation will be achieved by eliminating barriers such as access to medications, quality of care, training of nurses, health education, and stigma.

Here in this review, some actual findings related to hypertension nursing published in the last decade in international articles are given.

Hypertension is the major risk factor for mortality in the world (Vedanthan et al., 2014). Quarter of the global adult population has hypertension and is patient number is likely to increase to 29% in 2025. Projection models indicate 1,2 billion hypertensive patients will be in developing countries in 2025 (Mittal & Singh, 2010). Currently, one third of people with hypertension are undiagnosed. Also half of diagnosed people are not taking medications. According to WHO (The World Health Organisation), high blood pressure results with nine million people deaths worldwide every year (Kitt et al., 2019). Hypertension is the major preventable contributor of cardiovascular morbidity and mortality (Spies et al., 2018). This diseases is the most important public health problem (Urbanetto et al., 2015) and

improvement of the self-efficacy and quality of life of patients with this diseases is essential (Khademian et al., 2020).

2. Nursing

Elevated blood pressure control rates is very low and many literature supports strategy of task redistribution of hypertension care to nurses (Vedanthan et al., 2020). Hypertension requires continuous long-term care to delay or prevent associated complication developments (Mattei da Silva et al., 2020). Adequate control of blood pressure reduces the risk of recurrent stroke (Kerry et al., 2013). Nurse-led hypertension management is effective and feasible to improve the outcomes of patients with uncontrolled blood pressure (Zhu et al., 2018).

Continues rise of hypertension worldwide is placing high social, economical and health burden on the sufferers, their dependants and health care providers. Disorders of the cardiovascular and renal systems are primary sources of hypertension. Lifestyle changes is advised to arrest progression to more severe hypertension and avoid more serious complications. A drug algorithm is also proposed by experts, in addition to the lifestyle changes, for the safe and effective management of antihypertensive medication. Specialist nurses appropriately trained in drug prescribing and working in hypertension nurse-led clinics could be an effective alternative to conventional approaches in the management of patients with hypertension (Chummun, 2011).

Poor treatment and control of hypertension in low- and middle-income countries is due to several reasons, including insufficient human resources. Nurse management of hypertension is a novel approach to

address the human resource challenge. Nurse management of hypertension is a potentially feasible strategy to address the human resource challenge of hypertension control in low-resource settings. However, successful implementation will be contingent upon addressing barriers such as access to medications, quality of care, training of nurses, health education, and stigma (Vedanthan et al., 2016). District nurses frequently encounter patients requiring blood pressure monitoring, lifestyle counsel and support. Empowerment as a method enables patients to both increase their control over their health and improve it. Nursing interventions through district nurses' counsel and support with empowerment improved patients' health (Rasjö Wraak et al., 2015).

In a study of Zhu et al., (2014), total 73 recruited participants were divided into two groups where a group received home visit and 2-4 telephone follow-ups by nurses. The control group received doctor-led hypertension management. After 8 weeks blood pressure readings, self-care adherence, self-efficacy, quality of life and patient satisfaction were measured. The group led by nurses had significant improvement in self-care adherence, patient satisfaction post-intervention compared to the control group led by doctors. Instead, no significant differences in blood pressure readings, quality of life and self-efficacy were observed between two groups. Findings revealed that nurse-led hypertension management is a promising way to manage hypertensive patients at the community level.

Park & Kim, (2016) examined the impact of nurse-led home visitats for hypertension self-management in older Koreans. Visiting nurses assisted elders with hypertension through home visits for 2–4 months. Total 13,452 hypertensive persons over the age of 65 completed the intervention. All outcomes were significantly improved and included blood pressure monitoring, hypertension knowledge, dietary management, medication adherence, self-confidence and self-management of hypertension. Nurse-led home visitation intervention can be helpful in self-management skill building among hypertensive elders. The program may improve medication adherence and health-promoting behavioral changes.

Hypertension is a silent disease of the masses with an increasing prevalence and poor control rates. Miao et al., (2020) tested the efficacy of nurse-led hypertension management with 156 hypertensive patients. A group received a 12 week period of hypertension management in which blood pressure of patients had greater improvement in self-care behaviors and a higher level of satisfaction with the hypertensive care compared to the control group. The nurse-led hypertension management model was found feasible and effective for patients having uncontrolled blood pressure.

Poor control of, hypertension is associated with a number of diseases, such as stroke, heart and renal failure, and high, mortality rates. Home blood pressure monitoring is the most significant predictor for improved, systolic blood pressure (Chiu et al., 2010). Nursing carries a large responsibility in care delivery to hypertensive individuals (Silva

et al., 2010). Nursing in hypertension care comprises counselling about lifestyle changes, blood pressure measurement, and being a translator for the physician. For the patient, changing lifestyle means performing self-care (Drevenhorn, 2018). Nursing care plays a prominent role in determining the overall satisfaction of patients' hospitalization experience. Studies have shown that satisfaction with nursing care is the best indicator of patients' satisfaction with healthcare facilities (Kasa & Gedamu, 2019).

The role of the nurse in improving hypertension control has expanded over the past 50 years. Involvement of nurses began with measuring/monitoring blood pressure and patient education to improve blood pressure control. Today roles of nurses and practitioners involve all aspects of care in hypertension management. These include detection, referral, follow up, diagnostics management, medication management, patient education, counseling, skill building, coordination of care, clinic management, office management, population health management, performance measurement and quality improvement (Himmelfarb et al., 2016).

3. Team-based care

Multidisciplinary teamwork has become an essential component in the care of patients with chronic conditions across the world (Vegesna et al., 2016). Team-based care is one of the key components of the patient-centered care. Teams involving pharmacists or nurses can significantly improve blood pressure control. This finding was determined by many meta-analyses and systematic reviews. Reviews indicated that team-

based care reduce systolic blood pressure by 4–10 mm Hg over usual care (Carter et al., 2012).

The patient-centered, multidisciplinary team is a key feature of effective care models that have been found to improve care processes and control rates. In addition to their clinical roles, nurses lead clinic and community-based research to improve the hypertension quality gap and ethnic disparities by holistically examining social, cultural, economic, and behavioral determinants of hypertension outcomes and designing culturally sensitive interventions to address these determinants (Himmelfarb et al., 2016).

In today's environment, organizational delivery systems must produce high-quality, efficient, and costeffective services (Kutzleb et al., 2015). Nurses play a major role in overall health by providing educational interventions to help improve self-management outcomes (Gorina et al., 2018) and occupy a central position in today's increasingly collaborative health care teams for a premium quality patient care (Propp et al., 2010). Appropriate and effective critical thinking and problem solving is necessary for all nurses in order to make complex decisions that improve patient outcomes, safety, and quality of nursing care (Sinatra-Wilhelm, 2012).

Nurses in primary health care settings are key stakeholders in the diagnosis and management of hypertensive patients. Unfortunately, the working conditions of nurses predispose them to stress, long hours of work, shift duties and unhealthy diets. Yet nurses are often overlooked

in health screening exercises, primarily because they are assumed to be informed and healthy (Monakali et al., 2018).

Medication-related problems are common among home care clients who take many medications and have complex medical histories and health problems. By partnering a pharmacist as a member of home care team may be very beneficial (Reidt et al., 2013).

Up to 20% of hospital-related adverse events are the result of communication-related misunderstandings (Raingruber et al., 2010). Hospital health services cannot be separated from nursing services which have a role in improving the health status of patients. The team method is the organization of nursing services using a team consisting of groups of clients and nurses. Nurse performance is a measure of the quality of service in a hospital. Performance is influenced by individual variables, psychological variables and organizational variables (Hasibuan et al., 2021).

High-risk patients have complex medical and psychosocial issues. Intensive outpatient primary care programs focusing on high-risk patients can have positive effects on end-of-life planning and care. In order to enhance care for high-risk patients, many health systems are implementing intensive outpatient programs, often with advanced practice nurses taking the lead. Nurse practitioner–led intensive outpatient primary care may increase hospice referrals for high-risk patients near end-of-life (Hummel et al., 2017).

Dehmer et al., (2016) estimated the prospective health, economic, and budgetary impact of universal adoption of a team-based care

intervention model for hypertension patiens in the United States via a simulation. They determined that 4.7 million (13%) fewer people with uncontrolled hypertension and 638,000 prevented cardiovascular events would be expected over 10 years. Estimated net cost savings for Medicare approached $5.8 billion. Net costs were especially sensitive to intervention costs.

4. Conclusions

Hypertension requires continuous long-term care to delay or prevent associated complication developments. Nurse-led hypertension management is effective and feasible to improve the outcomes of patients with uncontrolled blood pressure. Multidisciplinary teamwork has also become an essential component in the care of patients with hypertension. Successful implementation will be achieved by eliminating barriers such as access to medications, quality of care, training of nurses, health education, and stigma. Intensive outpatient primary care programs focusing on high-risk patients can have positive effects on end-of-life planning and care.

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CHAPTER 9

WITHOUT PHILOSOPHY, MENTAL HEALTH SCIENCE AND PSYCHOLOGY AS WE KNOW IT WOULD NOT EXIST

Lecturer Dr. Z. Deniz AKTAN[1]

[1] Işık University, Faculty of Economics, Administrative and Social Sciences, Psychology, Istanbul, Turkey, deniz.aktan@isikun.edu.tr, Orcid ID:0000 0003 1757 2024.

INTRODUCTION

It is obvious that every science starts with a question and over recent years, philosophy has been the source of these questions with its unlimited answers and its newly created questions. It can be said that philosophy has always created new frameworks for new sciences with its endless questions, and psychology is one of those, which was created and improved by the unlimited questions of philosophy. When taking this into account it can be claimed that present day psychology owes its existence to the science of philosophy. Thus, this work attempts to analyse the question "whether or not the psychology as we know it would exist without philosophy" by first defining both sciences. Then it will try to analyse the first philosophers, who were interested in the science of psychology, and finally it will attempt to discuss the relationship between psychology and philosophy.

1. HISTORY OF PSYCHOLOGY

Although psychiatry was first described by the German medical professor Reil in the early 1800s (Cookson, 2012), modern psychology, which is interested in human and animal behaviours and their cognitive process, was first established by Wilhelm Wundt in 1879 in Leipzig (Bermudez, 2005). According to Plotnik (2005) psychology was born through an effort which tries to understand human behaviours; however its effort does not refer to understanding spiritual relationships, thus it is believed that psychology is one of the positive sciences. On the other hand, when the history of philosophy is analysed, it is obvious what a

great history philosophy has. Moreover, this analysis shows how the other sciences have been enlightened by the varied questions of philosophy. The main difference between philosophy and psychology is their aspects such as subjectivity and objectivity. Since, the statements of philosophy which are related to human nature are significantly subjective, like its other explanations which refer to another science field. However, as mentioned before, psychology is a positive science in which facts are studied and it tries to find out casual relations in behaviour by using the methodology of science (Sharma & Chandra, 2004).

1.1. The Relationship Between Body and Mind

When the literature examined, it can be seen that the first studies on the concept of body and mind are based on the ancient age Greek philosophers. Weber & Thilly (1896) stated that the ancient age philosophers believed the spirit is dependent upon matter; they handled the spirit as a matter such as water, earth or fire. However, Plato claimed that the spirit is a power which does not depend on a matter for its existence. Then, Aristotle improved his teacher Plato's approach by combining it with the Hippocrates's statements, and claimed that the spirit is a functional part of the human body. In addition, he pointed out that the heart is the most appropriate place to the internal way of living. It is obvious that the science of psychology has been affected by Aristotle's approach as have other sciences; and it can be said that this is the first statement which has been seen as a guide for scientific psychology (Bermudez, 2005; Weber & Thilly, 1896). When taking

these approaches and statements into account it will be obvious that both these sciences were first engaged by Aristotle.

1.2. Hippocrates and first Clues on the Relationship between Body and Mind

Although Aristotle was the first philosopher who study on the relationship between body and mind at a scientifically acceptable way, it's known that, the first discourses on the relationship between mental health and physical health are based on Hippocrates. Specifically, in previous work Havier (2014) mentioned about Hippocrates' "Four Humours Theory". In fact, the roots of this theory based on ancient Egypt. Moreover, it is even said that the cornerstones of the theory were laid initially by pre-Socratic Greek philosophers such as Anaximander, Pythagoras, and Alcmaron, and Hippocrates created this theory inspired by these philosophers (Havier, 2014). According to this theory, there are 4 basic fluids that create the human body; yellow bile, black bile, phlegm (mucus or mucin) and blood (or red bile). In this theory, when Hippocrates mentioned about black bile, he described melancholia and gave the first clues about the relationship between mental health and physical health. Thus, these works of Aristotle and Hippocrates laid the groundwork for "the body and mind theory" defined by Descartes in the 17th century (Clarke; 2006; Havier, 2014; Türk, 2017).

1.3. Descartes and the Birth of Body and Mind Theory

In the first decades of the 17th century the French philosopher Descartes attempted to explain the relation between the body and the mind. Although he was a mathematician he was interested in the human mind and its components. Moreover, he claimed that the body and mind are separate and thus the dualism approach was born (Clarke, 2006). Therefore, several researchers believe that he is the first psychologist in the world (Bermudez, 2005). According to Descartes the human body is a mechanism, which is a material and tries to adapt to the laws of nature. However he pointed out that the mind is a nonmaterial piece of the human body which can evaluate the external and internal life of the mechanism. Descartes started to discuss this relationship which is between the neural system and human behaviour, by using the science of physiology. However when he tried to establish a global world by writing one of his important books, "The World" he guided not only the physiology and the physic sciences, he also guided the psychology science (Bermudez, 2005; Gabbay, Thagard & Woods, 2007).

2. FROM PHILOSOPHY TO THE BIRTH OF MODERN PSYCHOLOGY

According to Clarke (2006), Descartes believed that some of the physiological problems caused psychological issues, because the mind and body interact with each other. After Descartes' ideas, it was necessary to focus on the physiological interaction of body and mind and these statements will have affected the birth of the modern

psychology approach in the late years of the19th century (Clarke, 2006). Moreover, Clarke stated that Descartes' muscular physiology model was the most effective reason for the engagement of biology and psychology sciences, and this was the other important impact on the birth of modern psychology. It can be said Descartes' beliefs gave psychology an opportunity for being a member of the science family in the future. In addition, it is believed that in the case of Descartes' statements, the advancements in physiological science affected the developments of scientific psychology in the world of science (Bermudez, 2005; Gabbay et al., 2007).

Additionally, in their previous study Gabbay et al. (2007) demonstrated that empiricism, positivism and materialism were the other philosophical movements, which affected the European aspects and had several effects on the development of psychology science in the 19th century. Several philosophers attempted to focus on the experimental method for understanding the mind processes in the 19th century Europe. A considerable amount of them tried to find out the relation between the body and its effects on the mind process by using the physiological methods (Gabbay et al., 2007). Weber and Fechner took the first step to establish the science of psychology by creating the Weber- Fechner Law (Plotnik, 2005). They attempted to analyse the relationship between the magnitude of a stimulus and the intensity that people feel, and this work was another impact on the birth of modern psychology. Then in the second half of the 19th century the first experimental psychology laboratory was established by Wundt, thus

psychology was separated from philosophy as a special science (Plotnik, 2005). When taking this into account it can be said that these effects of philosophy and physiology help the development of the science of modern psychology.

2.1. The Birth of Modern Psychology Science and its Relations with Philosophy

After its transformation from philosophy to psychology science, different psychology approaches were established within this new science such as behaviourist, cognitive, physiological and psychodynamic approaches (Plotnik, 2005; Morris & Maisto, 2005). However, the effects of philosophy on psychology came into question again in the early years of the 20th century by Carl Gustav Jung, who was an advocate of the psychodynamic approach in his early works. Before Jung has established his own psychology approach, he had worked for six years with his colleague Sigmund Freud. In 1914 he created his own approach, which is called the analytical psychology approach. Nowadays, it is known that Jung's theories were particularly affected by some aspects of philosophy (Stevens, 1994; Bermudez, 2005).

According to Woon Ko (2011) Jung's works were undeniably affected by philosophy, especially his collective unconscious theory, archetypes, anima-animus and the synchronicity theory have so many elements of philosophy. Moreover the researcher states that Jung used philosophy to establish his theories and then he utilized it to combine his ideas. For

instance, in his synchronicity theory he claimed that there are some cases, which occur at the same time unboundedly, and he believed that there is a relationship between these cases. Jung stated that although it looks like there is no relation between different parts, there is actually a relationship between chaotic parts, which belong to an unknown entity. For instance, when somebody has a dream which is about a friend, it comes true in real life, thus he believed that there is a relation between dreams and real life experience (Woon Ko, 2011). Over the last decades several psychologists believed that these kinds of facts were only a coincidence; but Jung states that there are the signs, which show how we engage with other people, and in general meaning how we engage with nature by using the collective unconscious (Stevens, 1994). In addition Woon Ko (2011, p. viii) expresses this situation "to examine the validity of his principle of synchronicity, Jung appeals to the philosophical systems of Gottfried Wilhelm Leibniz (1646-1716), Immanuel Kant (1742-1804), and Arthur Schopenhauer (1788-1860)". It is obvious that philosophy has significantly affected Jung's analytic psychology approach and it can be said that without philosophy, Jung's theories wouldn't exist.

CONCLUSION

In conclusion, it can be said that philosophy consists of different aspects of science and the scientific approaches, thus it is obvious that without science philosophy would be only a spirit without the body. However, sciences also need philosophy to complete their development and without philosophy they would be only a sapless body. When taking

this in to account it is obvious that every psychological approach creates its own philosophical movements, thus psychology and philosophy cannot be separated. Consequently, it can be said that every psychologist has to have an interest in philosophy, as a matter of fact they need to use it in their daily life; they should not only be a scientist they should also be an amateur philosopher.

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CHAPTER 10

EPIDEMIOLOGY, DIAGNOSIS AND TREATMENT OF LIVER ECHINOCOCUS GRANULOSUS

Op. Dr. Felat ÇİFTÇİ[1]

[1] Şanlıurfa Training and Research Hospital, General Surgery, Şanlıurfa, Turkey, felatciftci@gmail.com.ORCID ID: 0000-0002-8958-7121

ACCESS

Echinococcal disease is mainly caused by the metacestode stage of Echinoccocus. Although 4 types of echinococci cause infections in humans, the most common type is Echinococcus Granulosus. E. multilocularis causes alveolar hydatid cyst in humans (1). In the infection of this species, cystic lesions occur in the organ where it is located, but it most often settles in the liver. Except this; It can also settle in other organs such as lung, brain, spleen, kidney, extremities, breast. The first radiological diagnosis of these

examination is USG. In cases where USG is insufficient, CT or MRI should be performed. The features of these cysts are radiologically standardized by the Gharbi classification. In addition, LgE and LgG eliza are examined for the diagnosis of cysts as a laboratory. While the sensitivity of these tests in liver cysts is between 80-90%, this rate decreases to 45% in lung and other cysts(2-5). Treatments of liver cysts include medical, PAIR and surgical treatment or various combinations of these.

DIAGNOSIS

In approximately 60-85% of hydatid cyst cases, the liver is affected in 25%, the lung and in a small part the spleen, brain, kidney, breast and extremities are affected. Cysts in the liver often reach large sizes at the time of diagnosis. Most of them are detected either incidentally without any symptoms, or when complications occur after opening to the biliary tract, peritonitis after free rupture, or pulmonary fistula.(1). In cases of

lung involvement, it is most commonly detected with symptoms such as cough, chest pain, hemoptysis and shortness of breath. (2,3).

1. RADIOLOGY

Imaging methods such as ultrasonography (USG), computed tomography (CT) and magnetic resonance (MRI) are used in the diagnosis of hydatid cyst. Especially in the diagnosis of liver hydatid cyst, the first of the imaging methods is USG. It can also be used for screening in endemic areas because it is noninvasive, easy to access and does not contain radiation.

1.1.USG

Ultrasonography, especially in the diagnosis of intra-abdominal hydatid cysts, is the first imaging method and its sensitivity is around 90-95%. (4). It can also be used for screening purposes due to its easy accessibility and lack of radiation exposure in endemic areas. Serology tests may also be required to support the diagnosis.(5). It is most commonly seen as a smooth round cyst on USG. It can be seen in various forms according to the stages of the cyst. In addition, they are classified as active, transitional or inactive according to their biological activities in ultrasonography. According to this classification, treatment modalities vary. To mean inactive cyst; There should be an elliptical cyst collapsing due to the decrease in pressure in the cyst, separation of the germinative layer from the cyst wall (water lily sign), development of calcification in the wall of the cyst, and coarse echolarin in the

cyst.(4). This classification of the cyst determines the type of treatment. Ultrasonographically, hydatid cyst is classified in 2 ways.

World Health Organization Classification:

DSÖ Aşaması	Explanation	Phase	Dimension	Treatment	alternative therapy
CE1	Unilocular unechoic cystic lesion with double line sign	Active	<5cm	Albendazole alone	PAIR
			>5cm	Albendazole + PAIR	PAIR
CE2	Multiseptated, "rosette-like" "honeycomb" cyst	Active	Any	Albendazole + either modified catheterization or surgery	Modified catheterization
CE3a	Cyst with detached membranes (water-lily sign)	Transitional	<5cm	Albendazole alone	PAIR
			>5cm	Albendazole + PAIR	
CE3b	Cyst with daughter cysts in solid matrix	Transitional	Any	Albendazole + either modified catheterization or surgery	PAIR

CE4	Cyst with heterogenous hypoechoic/hyperechoic contents; no daughter cysts	Inactive	Any	Observation	-
CE5	Solid plus calcified wall	Inactive	Any	Observation	-

According to the World Health Organization classification, CE1 and CE2 are viable cysts, CE1 is unilocular and CE2 is multilocular cysts containing daughter vesicles. CE3 is divided into two types. CE3A are transitional cysts with impaired membranes. CE3Bise contains daughter vesicles with solid matrix. CE4 and CE5 are dead cysts and often do not require treatment.(6).

World Health Organization Classification (7)

a- Gharbi Classification:

It was revealed by Hassen A. Gharbi et al. in 1981 as a result of a study on 121 cases. It is a classification that divides hydatid cyst into 5 classes according to its ultrasonographic features.(8). According to this:

Type I: It is pure liquid and cystic structure. Cysts appear as an anechoic collection. The wall of the cyst is not prominent.

Type II: Cysts with prominent walls and floating membranes. The disintegrated wall here must be sought in those with any intrahepatic fluid, as this is almost pathognomonic for a hydatid cyst.

Type III: The most distinctive feature of this type is the presence of chambered cysts with prominent echoes and "honeycomb" appearance. An increase in echo within the cyst indicates the presence of simple or multiple secondary vesicles. In addition, the wavy appearance in the cyst indicates the presence of the separated and folded membrane.

Type IV: This type of cyst appears as a roughly round mass with irregular contour and echo pattern. In addition, the simultaneous appearance of cysts in the liver or another organ with different echographic patterns is typical. The cyst is not alive.

Type V: This type appears as a formation with a very hypermechoic contour and a cone-shaped shadow that is usually outlined to some degree. The cyst is not alive.

1.2. Computed Tomography

Computed tomography (CT) is the best imaging method to determine the number, diameter and anatomical location of cysts and is better than US in detecting extrahepatic hydatid cysts. (9). The sensitivity of CT in the diagnosis of echinoccocus is higher than USG (95-100%). CT is the best imaging method in choosing both the treatment method and the surgical technique if surgery is to be performed. It gives detailed information about the localization of the cyst in both the liver and other

organs. It also gives detailed information about the neighborhood of the cyst to the vascular structures, its relationship with the bile duct, and its neighborhood relations. In addition, it may be superior to USG in terms of intrabiliary or free wall rupture and other intra-abdominal complications.(10). USG may be superior to CT in showing cyst wall hydatid sand and juvenile cysts. However, CT is superior in showing gas and calcifications within the cyst or mapping the cyst. (11). Magnetic Resonance (MRI) has no superiority over CT in the diagnosis of hydatid cyst. On the contrary, it is not recommended due to its high cost unless another differential diagnosis is considered. (12,13).

In addition, ERCP (endoscopic retrograde cholangiopancreatography) or MRCP (magnetic resonance cholangiopancreatography) are used to detect the relationship of the cyst with the liver biliary tract, to detect postoperative biliary fistula or to evaluate treatment options if related.(14,15).

2..LABORATORY

Many diagnostic tests are used in the diagnosis of hydatid cyst. These are used in the primary diagnosis and in the follow-up of relapse after treatment. At the beginning of these; Indirect hemagglutination (IHA), latex agglutination, indirect immunofluorescence, ELISA (Enzyme-Linked ImmunoSorbent Assay) and complement fixation test are available. In a series of 79 cases in patients with postoperative proven hydatidosis, IgG ELISA was found to be the most sensitive test with 84%. In addition, the specificity of all tests in this study was between

98-100%.(16). In general, the immune response of the liver against cysts is higher than lung cysts. For this reason, the sensitivity of tests in the liver is around 85-90%, while the sensitivity of tests in the lungs decreases to 65%.(17). In this direction, in a study conducted with a series of 243 cases, the sensitivity of ELISA (IgG, IgE) tests in liver cysts was 89%, while the sensitivity of those in the lung was 78%. (18). Among these tests, IHA and ELISA tests are the most frequently used ones for screening purposes.

Liver	IgG ELISA: 80-90%
	IgE ELISA: 82-92%
	Latex agglutination: 65-75%
	Hemagglutination: 80-90%
	Immunoblot: 80-90%
	Enzyme Associated Immunotransfer blot: 80%
Lung	IgG ELISA: 60-85%
	IgE ELISA: 45-70%
	Latex agglutination: 50-70%
	Hemagglutination: 50-70%
	Immunoblot: 55-70%
	Enzyme Associated Immunotransfer blot: 55%

3. DIFFERENTIAL DIAGNOSIS

In general, a cyst, cystic-solid, or solid-occupying lesion anywhere in the body can be confused with a lesion at any stage of a hydatid cyst. (19). In the differential diagnosis; liver simple cysts, hemangiomas, hepatoblastoma, HCC, abscess, colon ca metastases, tbc etc. There is any lesion with mass effect(19).

It can be confused with simple cysts of the liver. Tension pain can be seen in these cysts, usually subcapsular ones, and nausea and vomiting depending on their localization. It is usually asymptomatic. USG or CT can be used in the differential diagnosis.

Hemangiomas are usually asymptomatic and detected incidentally. The most common clinical findings are abdominal pain and a feeling of fullness. USG or CT is sufficient for the differential diagnosis. Dynamic MRI can be used for diagnosis in those who cannot distinguish clearly. (20).

Hepatocellular carcinomas are also usually asymptomatic at first. In the later stages, it may give clinical symptoms due to mass effect and biliary tract or vascular compression. Since most of them develop on the basis of cirrhosis, it can progress with the symptoms of cirrhosis.(21). It can give symptoms in the form of abdominal pain and a feeling of fullness. It can be differentiated from hydatid cyst by imaging methods (CT, MRI) and clinical signs and biochemical tests (AFP, ELIZA, etc.)(22). Liver and lung abscesses can also be confused with hydatid cyst in terms of both appearance and echo. With aspiration in liver abscesses,

Differential diagnosis can be made with bronchoscopy in lung abscesses. Separator Although immediate aspiration is important, it should not be the first option. Anaphylaxis It may be preferred in cases where imaging (USG, CT, MRI) is insufficient due to ischemia. It is very difficult to make the differential diagnosis of infected hydatid cysts from abscess.(23).

3. CLINIC

Although hydatid cyst is mostly asymptomatic, clinical symptoms mostly vary according to its location, number, diameter, type, neighborhood, and relationship to the biliary tract and bronchi. Cysts in the liver are mostly asymptomatic. It usually does not give clinical symptoms before it reaches 10 cm in diameter. Depending on its relation to the biliary tract, complaints of tension, pain, nausea and vomiting, and itching can be seen in the right upper quadrant of the abdomen. In addition, a cyst opened to the biliary tract may cause cholangitis, pancreatitis and anaphylaxis complaints(24).

Hydatid cyst in the lung may cause clinical symptoms such as shortness of breath, cough, chest pain and hemoptysis. (3,25).

Hydatid cysts located in the brain can cause seizures, mostly by increasing intracranial pressure(26). Kidney cysts can cause complaints such as hematuria, burning in the urine, hydronephrosis (27).

4.TREATMENT

Liver hydatid cyst basically consists of 3 different stages or their combinations. These; medical treatment, PAIR and surgery. (6,7)(19).

2.1.Medical Treatment

While determining the treatment standards, the radiological cyst classification determined by the World Health Organization (WHO) is taken as a basis(7). In general terms, since CE1 and CE3A cysts have only one compartment, the treatment option for those with <5 cm is medical and albendazole is given at a dose of 10-15mg/kg. PAIR + albendazole combination is the standard treatment option for cysts >5 cm in this class.(7).

Albendazole (10-15mg/kg), especially in the treatment of liver hydatid cysts, is the best option, and in cases where this is not available, mebendazole or praziquantel is used as an alternative(28). CE2 and CE3B cysts are not suitable for PAIR procedure because they consist of more than one chamber. Because such cysts have a high relapse rate after the procedure. The primary treatment for these cysts is the combination of andazol + surgery. One week before surgery, andazol 10-15mg/kg is started. This treatment was continued for 1 month after surgery.

For CE4 and CE% type cysts, follow-up is recommended unless there are clinical signs. (7).

2.2.PAIR Treatment

It is the preferred treatment in combination with medical treatment, especially in CE1 and CE3A type cysts. It can be done for both diagnosis and treatment purposes. (29). In this procedure, the cyst is aspirated by inserting a needle into the cyst. Then, 20% serum saline is injected into the cyst. After waiting for 20 minutes, the cyst is reaspirated again. In this procedure, the cyst should be entered intraparenchymally to prevent perforation and anaphylaxis(30). PAIR procedure is not preferred because of the high recurrence rate in CE2 and CE3B type cysts consisting of more than one chamber. In suitable cases, the full cure rate is around 95% (31,32).

2.3. Surgical Treatment

Surgery is preferred for cysts that are not suitable for percutaneous treatment, such as CE2 and CE3B. Apart from this, surgery is preferred as a treatment option for cysts >10 cm in size, perforated cysts, cysts opened to the biliary tract, cysts causing anaphylaxis and cysts causing secondary infection (33)(7).

The main goal in surgery should be the complete removal of the cyst. In cases where this is not possible, the inside and remaining part of the cyst should be thoroughly disinfected with saline. During surgery, great care should be taken to prevent the cyst from spilling into the abdominal cavity. When such a situation develops, the intra-abdominal serum should be washed with saline (34–36). In a patient who is considered for surgery, 10-15mg/kg albendazole treatment should be started one

week before the surgery and for one month after the surgery. This period can be extended according to the postoperative follow-ups. Complications such as secondary infection, intra-abdominal abscess development, sclerosing cholangitis, anaphylaxis, and recurrent cyst due to shedding of the cyst may develop after surgery (37,38).

Surgical technique should be decided entirely according to the experience of the surgeon. Laparoscopic cyst excision can be considered as an alternative surgical method in experienced surgeons. Apart from the standard advantages of laparoscopy (early mobilization, early discharge, early return to work, low wound infection), randomized studies comparing its superiority over open surgery have not been conducted (39). Laparoscopic surgery should be preferred especially for cysts located anterior to the liver (40).

6. CONCLUSION

Liver hydatid cyst is a disease caused by a parasitic infection called Echinococcus, which settles as an intermediate host in the human liver. There are four types: Echinococcus Granulosus, Echinococcus Multilocularis, Echinococcus Vogeli, Echinococcus Oligartus. The most common is E. Granulosus. Radiologic methods such as USG, CT and MRI and tests such as latex hemagglutination, ELISA are used in the diagnosis. Although it most often settles in the liver (2/3), it can also settle in organs such as the lung (25%), brain, spleen, and kidney. It is divided into 5 types according to the radiological classification of the World Health Organization. Treatment options are determined according to these types. There are treatment options such as medical treatment, PAIR, surgical treatment and their combinations. Albendazole is most commonly used in medical treatment. Apart from that, mebendazole and praziquantel are alternative drugs. It may cause complications such as secondary infection, intra-abdominal abscess, anaphylaxis, and sclerosing cholangitis. The choice of surgical techniques (laparoscopic and open technique) should be decided according to the experience of the surgeon. It should be taken out with as little contamination as possible and without disrupting the integrity of the cyst.

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CHAPTER 11

THE MOST COMMON PROBLEMS IN THE NEWBORN BABY AND THE TRADITIONAL PRACTICES

R.A. Ebru ERTAŞ[1], R.A. Feride ÇEVİK[2]

[1] Kutahya Health Sciences University, Faculty of Health Sciences, Midwifery Department, Kutahya, Turkey, ebruu_ertas@hotmail.com, 0000-0001-7749-7033
[2] Eskisehir Osmangazi University, Faculty of Health Sciences, Midwifery Department, Eskisehir, Turkey, feride__94@hotmail.com , 0000-0001-6799-7050

INTRODUCTION

Pregnancy is a special process that prepares a woman for motherhood. With the birth, the woman has opened a new page in her life. In the postpartum process, a woman may experience feelings such as joy and excitement, as well as some concerns about the process of getting used to the baby and caring for the baby. This condition can cause psychological and social changes on the woman. In addition to the physical or psychological changes of the mother after childbirth, some problems may also occur in the baby. These problems include conditions such as frequent crying, gas pains, and skin problems, especially. It has been reported that the most common problems in the newborn baby are gas pains, diaper rash, thrush, jaundice and dandruff. (Guzel et.al., 2017). For the mother who is preparing for the baby care process, these problems in the newborn increase the level of anxiety. Mothers who do not want to use medical drugs unconsciously to solve these problems are increasingly resorting to traditional methods. Midwives who support mothers in caring for their babies during the postpartum process provide guidance on such traditional practices.

In this review article, it is aimed to investigate the most common problems in the newborn baby and the traditional practices used to solve these problems by scanning the literature.

1. GAS PAINS (INFATILE COLIC)

Infantile colic, which is expressed as gas pains among the people, is a condition that manifests itself with severe and uninterrupted crying in newborn babies, attacks in the evening hours, the baby pulling his legs to his stomach, clenching his fists and hardening in the abdomen. Gas pains/infantile colic affect 5-19% of healthy babies worldwide. Although the causes are not yet clearly known, it is reported that it occurs due to gastrointestinal, psychosocial and central nervous system-related causes. The problem of gas pains/infantile colic passes by itself after 3-4 months (Alagoz, 2013; Gelfand, 2016).

Among the traditional practices that mothers do for gas decubitus;

- Massaging the baby's feet and belly area with herbal oils,
- Wrapping the baby's feet and belly area with herbal oils,
- Wrapping the baby's navel with onions, cabbage and vinegar,
- Drinking the boil products such as fennel, anise, chamomile, cumin, mint as drops to the baby,
- Drinking vegetable oils as drops to the baby,
- Giving the baby a warm bath,
- Drinking soda to the baby,
- Cradling the baby, giving a pacifier,
- Running noisy appliances such as a vacuum cleaner or a hair dryer next to the baby,
- There are practices such as arson (Alagoz, 2013; Guzel et. al., 2017; Calbayram et. al., 2017).

It has been shown by randomized studies that traditional practices such as warm bathing, hugging the baby, running a vacuum cleaner / hair dryer to help solve the symptoms of gas pain /infantile colic do not have a positive effect. It has been reported that practices such as swaddling the baby, shaking the baby, massaging the baby, regulating the baby's sleep and feeding hours have a positive effect on reducing the symptoms of gas pains/infantile colic, but should be supported by further studies (Karabayir & Gokcay, 2017).

2. DIAPER RASH

Diaper dermatitis, popularly known as diaper rash, can be seen as inflammation of the skin in the perineum and sub-perineal region and as ulcer-like skin lesions. The use of diapers in newborn babies is a triggering factor for the formation of diaper rash. The skin of the newborn is different from the skin of adult individuals. The skin layer of the newborn's skin is thin, the skin has a lower water retention potential. It is observed in the first 4 weeks of life of newborn babies. The development of the skin barrier in the newborn remains incomplete until the baby is about 12 months old. Diaper rash is most often observed in infants aged 9-12 months (Sivri & Karatas, 2015; Mactaggart et. al., 2021). Its prevalence is reported to be 25%. (Lawton, 2020).

Among the traditional practices that mothers do for diaper rash;

- Salting the baby so that there are no diaper rash,
- Using baby powder to protect or treat diaper rash,
- Appling cream to the baby after washing and drying,
- Appling olive oil to the baby after washing and drying,
- Wiping the perineum area with soapy water,
- There are practices such as applying white soil to the perineum area (Cinar et. al., 2015; Sivri & Karatas, 2015; Guzel et. al., 2017; Ozdemir, 2020).

It is known that the practices of salting the baby for diaper rash can lead to consequences such as redness of the baby's skin, deterioration of skin integrity, fluid loss (Cinar et. al., 2015). The correct practices that can be done in case of diaper rash are to change the baby's diaper frequently and keep the area clean and dry, use products such as diaper rash cream with the advice of a doctor (Guzel et. al., 2017).

3. THRUSH

Oral candidiasis, popularly known as thrush, is a clinical diagnosis caused by the Candida Albicans group fungus, usually based on white spots dec the mouth. Although the etiology is not clearly known, it is estimated that the microorganisms that cause thrush provide vertical passage during vaginal delivery or horizontal passage from the environment. The fact that their immune system is weak makes babies prone to infection, while the fact that they do not have enough strength to cope with this problem can also cause complications. Its prevalence ranges from 4% to 15%. Thrush usually disappears on its own, but in

stubborn cases, medication may be required (Vainionpää et. al., 2019; Ozdemir, 2020).

Among the traditional practices that mothers do for thrush are;

- Wiping the baby's mouth with carbonated water
- Rubbing mother's hair or the hair of a mother with twin babies or an old woman's hair in the baby's mouth,
- Rubbing breast milk, flour and garlic or a mixture of breast milk, sugar and starch into the baby's mouth,
- Cleaning the baby's mouth with water,
- Rubbing soda into the baby's mouth,
- There are practices such as rubbing sugar, honey, molasses, black mulberry syrup, delight powder, starch, vinegar, olive oil, mineral water, lemon juice in the baby's mouth (Altay & Bicakci, 2019; Ozdemir, 2020).

It has been reported that wiping the baby's mouth with carbonated water and using medication with a doctor's recommendation are the right practices for the treatment of thrush (Guzel et. al., 2017). It can be said that the other practices mentioned above should be avoided because they can cause complications such as aspiration, skin integrity disorder and allergies in the baby.

4. JAUNDICE

It is a condition caused by a high level of bilirubin in the blood, which is observed at the end of the first 24 hours in newborn babies. It is

observed with a yellowish discoloration of the baby's skin, sclera and mucous membranes. More than 60% of healthy newborns develop neonatal jaundice, and hyperbilirubinemia is diagnosed within the first week after birth. Jaundice usually begins on the baby's face and spreads to his body after birth over time. As a result of excessive bilirubin levels, bilirubin can cross the blood brain barrier, causing damage to the brain, and the kernicterus table may develop. For this reason, jaundice is a serious condition that needs to be carefully monitored and taken precautions. The baby should be breastfed frequently and monitored closely by a doctor or midwifery (Pan et. al., 2017; Ozdemir, 2020).

Among the traditional practices that mothers do for jaundice are;

- Giving the baby a yellow blanket, wearing yellow clothes, wearing gold, or giving sugar water,
- Tying a yellow string or garlic to the baby's wrists or neck,
- Draining the baby's blood which by cutting the baby's forehead, behind the ear, between the two eyebrows, the inner ligament of the upper lip,
- Keeping the baby under a fluorescent lamp or sunlight,
- Washing the baby with poppy flower water, golden/crocus leaf water, spring water or egg white,
- Drinking to the baby mineral water with acid removed, apricot juice, male child urine,
- Dripping lemon into the baby's mouth,
- Taking the baby to places such as January/bed/ shrine,
- Feeding the baby with persimmon or chicken livers,

- There are practices such as dripping nasal blood into the baby's eye (Guzel et. al., 2017; Calbayram et. al., 2017; Altay & Bicakci, 2019; Ozdemir, 2020).

Such practices for solving jaundice should be avoided because they can cause different complications such as aspiration, bleeding, suffocation, allergy development in the baby. It has been reported that the most correct practices to be done for jaundice are to breastfeed the baby frequently and take it to the doctor (Guzel et. al., 2017).

5. DANDRUFF

In newborn babies, crusted skin parts that form as brown and / or yellow flakes in the upper layer of the scalp are called hosts. It can be observed in the first months of life, its prevalence ranges from 26% to 60%. Host care can be done with simple practices, but there is also the possibility of seborrheic dermatitis when neglected (Demirbag et. al., 2012; Guzel et. al., 2017; Ozdemir, 2020).

Among the traditional practices that mothers do for the mansion;

- Applying olive oil/baby oil to the baby's hair and washing it afterwards,
- There are practices such as applying a mixture of olive oil and baking soda to the baby's hair, waiting for a while and combing his head with a comb after washing (Guzel et. al., 2017; Altay & Bicakci, 2019).

From such practices made for the host problem, it has been reported that it is the right practices to apply olive oil to the baby's hair, it will be the right thing to take the baby to the doctor when the host problem occurs (Guzel et. al., 2017).

CONCLUCSION

As a result, it is important to notice problems such as gas pains, diaper rash, thrush, jaundice and host that are common in a newborn baby at an early stage and provide care with proven practices. Many of the traditional treatments for these problems can lead to serious conditions in the baby that result in complications such as aspiration, bleeding, suffocation, deterioration of skin integrity, and the development of allergies. It is important that midwives who support mothers with baby care during the postpartum process inform mothers about the complications that such traditional practices may develop in the baby and about providing care with proven practices for the problems experienced.

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CHAPTER 12

CLINICAL FEATURES AND PATHOGENESIS OF PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

Spec. MD., Furkan ASAN[1]

[1]Iğdır Devlet Hastanesi, Nöroloji Bölümü, Iğdır/Türkiye, furkan61asan@gmail.com, ORCID ID: 0000-0003-3062-5872

INTRODUCTION

Progressive multifocal leukoencephalopathy (PML) is a central nervous system (CNS) disease that occurs as a result of reactivation of the John Cunningham virus (JCV) and is usually fatal. PML, which was first reported in patients with hematological malignancies in the 1950s, started to be encountered much more frequently with the acquired immunodeficiency syndrome (AIDS) pandemic in the follow-up period. In the following years, its frequency began to decrease again with the widespread use of antiretroviral drugs that are effective against AIDS. However, in recent decades, with the frequent use of immunosuppressant drugs in many rheumatological, neurological, oncological and nephrological diseases, an increase in the frequency has begun to be observed again. In addition to PML, JCV granule cell neuronopathy (JCV GCN) and JC virus encephalopathy have also been described in recent years. In this section, mainly the disease of PML will be mentioned.

1. EPIDEMIOLOGY

PML is a disease that occurs in cases of immunosuppression, specifically cellular immunity, due to an underlying illness or drugs used. For this reason, there are variations in its frequency according to clinical conditions that cause immunosuppression. On the other hand, there are differences in the reported incidence rates since the incidence is very low, even in patients with immunosuppression. The incidence rate of PML in AIDS has been reported between 0.06% and 0.13% in studies conducted during the era of antiretroviral agents (Engsig et al.,

2009; Khanna et al., 2009). In a study conducted to determine its frequency in non-AIDS patients, the incidence rates were found to be 2.4 in systemic lupus erythematosus (SLE) per 100,000 people, 35.4 in bone marrow transplant patients, 8.3 in non-Hodgkin lymphoma, 11.1 in chronic lymphocytic leukemia, and 10.8 in autoimmune vasculitis (Amend et al., 2010). As can be seen, it is challenging to determine an exact incidence due to the very low incidence rate and the heterogeneity of the conditions that predispose to PML development.

PML has begun to be detected in multiple sclerosis (MS) patients with the frequent use of disease-modifying drugs (DMD) in the treatment of MS. Drugs with reported PML cases in this group are natalizumab, rituximab, fingolimod, and dimethyl fumarate. The drug with the highest risk of PML development is natalizumab, with an incidence rate of 0.1-1% (Berger, 2017). Therefore, close follow-up of patients using natalizumab in terms of PML and not using the drug for more than two years are recommended.

2. PATHOPHYSIOLOGY

2.1 JC Virus

JC virus belongs to the human polyomavirus family and is one of the first identified viruses in this family. Like all other polyomaviruses, it causes only asymptomatic infection unless the host is severely immunosuppressed (Moens et al., 2017). JCV, which has very high seropositivity in the community, is thought to be transmitted from person to person by inhalation or ingestion. It has been determined that

the positivity of JCV, whose carrier rate increases with age, is around 60-80% in the seventh decade (Knowles et al., 2003).

JC virus is a small, non-enveloped virus containing double-stranded DNA. The replication and protein synthesis of the virus that enters the cell is entirely dependent on the functional units of the host cell. Its circular genome consists of the early viral gene region, the late viral gene region, and the non-coding control region (NCCR) that separates these two regions (Pietropaolo et al., 2018). The NCCR is the most genetically diverse region in the genome of the JC virus and is responsible for cellular tropism. In addition, it has been reported that nuclear factor-1 (NF-1), one of the DNA-binding proteins in human cells, is also involved in the intracellular replication of the JC virus and that its cellular tropism develops according to the distribution of NF-1 subtypes in the body (M. C. G. Monaco et al., 2001).

JC virus is divided into two subtypes according to the genomic structure of the NCCR region. The type that is more common in environment and has a high genomic similarity is called archetype variant, while the type with significant genomic changes and neurotropic features is called the prototype variant. (Wollebo et al., 2015).

2.2. JC Virus Infection

The detection of JCV in the tonsillar tissue strengthens the possibility that the tonsils may be the primary site of infection (M. C. Monaco et al., 1998). But on the other hand, JCV has also been detected in gastrointestinal cells (Del Valle et al., 2005). As a result, JCV entering the body by inhalation or ingestion causes asymptomatic viremia in the

body. It also causes an asymptomatic persistent infection in the kidney and bone marrow, reaching the hematogenous route (Wollebo et al., 2015). Furthermore, the archetype JC virus with the same genomic sequence was found in urine samples taken from the same patients at different times. This observation suggests a persistent infection rather than recurrent JC infections (Kitamura et al., 1997).

K JCV, which enters the blood from the bone marrow or other organs, mainly infects leukocytes and is carried to other organs, especially the brain, via leukocytes (Dörries et al., 1994). It has been shown that the prototype variant is also present in leukocytes along with the archetype variant. Thus, the prototype variant is detected in a cell of human in the JCV life cycle for the first time. Although these findings support the idea that the prototype variant differs from the archetype variant in the body, no clear evidence has been found in this regard.

2.3. Development of PML

Although the seropositivity of JCV is quite common in the population, the incidence of PML is relatively low. This situation is because several events must occur together for the development of PML.

Firstly, the archetype variant, which is more common in the environment and the body, needs to be transformed into the prototype variant. The archetype variant does not have neurotropic properties, and it is known that the JCV variant in the PML cases studied is the prototype variant. The brain is not one of the primary areas where JCV infection develops. In a study conducted with MS patients, the JCV DNA was not found in the brain (Buckle et al., 1992). However, in

healthy people, JCV DNA fragments were detected in many brain regions, but there was no evidence that the virus was replicated (Perez-Liz et al., 2008). These observations point that JCV can migrate to the brain independent of its subtype, but this transmission is functionally insignificant in non-immunocompetent individuals.

The most appropriate candidate for localization for JCV subtype change is lymphoid organs. In non-AIDS PML patients, the JCV DNA sequence detected in bone marrow biopsies taken months before the development of PML was similar to the JCV DNA sequence from PML samples (Carson et al., 2009). In addition, JCV DNA, including its prototype variant, has been detected in bone marrow progenitor cells of healthy and immunocompetent patients (Major, 2010). Therefore, bone marrow is thought to be the most likely localization of the formation of the prototype variant of JCV (Pietropaolo et al., 2015).

PML developed explicitly in patients with suppressed cellular immunity. The cases of natalizumab-associated PML, a drug used to treat MS and inhibit the migration of T cells to the brain, provided us with unique information about the pathophysiology of PML. As a matter of fact, natalizumab does not create significant immunosuppression in the body and does not create an environment for other opportunistic infections. The increase in the risk of PML in these patients indicates that T cells that are prevented from entering the brain have an essential role in the pathophysiology of PML (Major, 2010). Natalizumab is also thought to cause an increased JCV viremia by

allowing progenitor CD34+ cells in the bone marrow to pass into the blood (Major et al., 2018).

Finally, in patients in whom the prototype variant develops and cellular immunity is suppressed, JCV replicates rapidly in the brain by primarily infecting oligodendrocytes. Virus replication, which causes oligodendrocyte dysfunction, appears clinically as progressive, focal demyelination areas (Berger et al., 2013).

3. CLINICAL PRESENTATION

There are different clinical presentation patterns in PML as to the counterpart of diffuse, progressive, and multifocal cerebral involvement. The most frequently reported clinical presentations are cognitive deficits, hemiparesis/hypoesthesia, speech disturbances, and visual complaints. Optic nerve involvement is not seen. Although spinal cord involvement is shown in pathological specimens, clinically myelitis has not been reported. Although PML is a white matter disease, epileptic seizures can be seen in approximately 1/5 of the patients (Lima et al., 2006). Patients with PML lesions very adjacent to the cortex have an increased risk of epileptic seizures (Lima et al., 2006).

Rarely PML can develop in patients without known immunosuppression. In this group of patients, low CD4 count or different idiopathic immunodeficiency conditions have been detected (Gheuens et al., 2010).

4. DIAGNOSIS

Today, the diagnosis of PML can be confirmed by cerebrospinal fluid (CSF) examination in an immunosuppressed patient with newly developed neurological deficits and typical radiological findings. CSF analysis is essential in a patient with clinical and radiological suspicion of PML. CSF is often devoid of cells. Even if cells are detected, their density is usually not more than 20 leukocytes/mm3. CSF protein is found to be increased in approximately half of the patients (Clifford et al., 2010). Detection of JCV DNA in CSF by PCR is essential for the diagnosis of PML. With the development of ultrasensitive JCV PCR methods, even very low copies (<10) of JCV DNA can be detected. The sensitivity of JCV PCR is reported to be >95% (Berger et al., 2013). On the other hand, low-copy JCV DNA was detected in the CSF in 2 patients who did not have PML and did not develop PML in the follow-up (Iacobaeus et al., 2009). Therefore, care should be taken about the false positivity of JCV PCR when the numbers of detected DNA are low. On the other hand, the absence of JCV DNA does not entirely rule out PML. In these cases, if there is ongoing clinical suspicion, a biopsy is required for a definitive diagnosis.

Brain biopsy exhibits the classical triad of PML, demyelination, enlarged oligodendroglial nuclei, and bizarre astrocytes. In addition, JCV DNA and JCV protein are detected in brain tissue (Berger et al., 2013).

4.1. Radiology of PML

Magnetic resonance imaging (MRI) is the most appropriate imaging modality for the diagnosis of PML. Multiple or single T2 hyperintense T1 hypointense lesions are seen in the white matter of the cerebrum or rarely brain stem, cerebellum, and white matter. None or minimal mass effect is present. Diffusion restriction is rarely seen. Contrast enhancement in lesions may be moderate in some cases. Contrast enhancement indicates an inflammatory response, and a better prognosis can be expected. It has been reported that contrast enhancement is higher in natalizumab-associated PMLs than in AIDS-related PMLs (Clifford et al., 2010). This is associated with a more robust immune response in MS patients than in AIDS patients and a stronger occurrence of immune reconstitution inflammatory syndrome (PML-IRIS). Lesions developing in different localizations over time may merge and become a single, large lesion.

5. TREATMENT AND PROGNOSIS

Due to the rarity of PML and the lack of an animal model, the number of prospective studies designed for its treatment is very few. The rapid and fatal course of the disease is another challenge in designing treatment studies. Treatment strategies can mainly be examined under two main topics. The first is direct antiviral treatments, and the other is to strengthen the antiviral response by reconstitute the impaired immune system.

Studies on cytarabine and cidofovir to reduce JCV DNA replication, on the other hand, with mirtazapine to block the entry of the virus into the

cell have not been found effective. Antimalarial mefloquine is another agent that has been shown to be ineffective (Cortese et al., 2020). Although it has been reported that maraviroc may be effective in the treatment of IRIS, larger studies showed controversial results (Sierra-Madero et al., 2014, p. 5). As a result, there is no direct antiviral that can be shown to be effective yet. Therefore, today's treatment approaches are primarily on the reconstitution of the immune response.

In AIDS-PML cases, which still make up the majority of PML patients, rapidly increasing the number of CD4+ cells with antiretroviral drugs are the mainstay in the treatment of PML. In cases of natalizumab or other immunosuppressant-related PML, early diagnosis and immediate discontinuation of the drug is the first step in treatment. Although it has been reported that plasmapheresis can be performed to accelerate the elimination of natalizumab after drug withdrawal, it has also been observed that this method may cause a more severe IRIS (Scarpazza et al., 2017).

Aside from AIDS and drug-related PML cases, it may not be possible to reconstitute the immune response in some patients. It has been reported that the anecdotal use of recombinant interleukin-7 and interleukin-2 in these patients may have a dramatic response (Gasnault et al., 2014; Przepiorka et al., 1997). However, there is a need for more extensive studies on the efficacy and safety of these treatment methods.

All immune reconstitution treatment modalities carry the risk of triggering IRIS. It has been reported that steroids may be beneficial in the treatment of IRIS because it is associated with increased

neurological deficits and mortality (Tan et al., 2009). However, steroids are not recommended for prophylaxis of IRIS as they may affect the antiviral response.

The prognosis of PML largely depends on the timing of diagnosis and the underlying etiology. Although mortality is between 20-25% in cases of natalizumab-associated PML, this rate is much higher in patients with irreversible immune system impairment such as hematological malignancies. In addition, among natalizumab-associated PML patients, 30% of survivors have severe neurological deficits (Clifford et al., 2010).

CONCLUSION

Since the 1950s, when PML was first described, significant progress has been made in its pathophysiology and treatment. However, there are still missing pieces of the puzzle regarding its pathophysiology and treatment. A better understanding of the life cycle of JCV may also reveal new approaches to direct antiviral therapies. It should be kept in mind that early diagnosis is the most important modifiable factor that determines prognosis and mortality, and close follow-up of patients in risky groups in terms of PML is of great importance.

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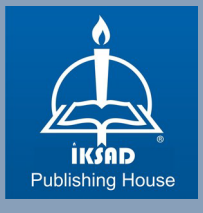

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