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Aims and Scope

The Journal of Pediatric Research is the official publication of Ege University and Ege Children's Foundation. It is a peer-reviewed journal published quarterly in March, June, September and December in English.

The Journal of Pediatric Research is a peer-reviewed, open-access journal, which publishes original research articles, invited review articles, clinical reports and case reports in all areas of pediatric research.

The journal publishes original research and review articles, which summarize recent developments about a particular subject based on standards of excellence and expert review and case reports. The target audience includes specialists in general pediatrics and pediatric subspecialties (Emergency Medicine, Allergy and Immunology, Endocrinology, Gastroenterology, Hepatology and Nutrition, Genetics, Cardiology, Hematology-Oncology, Infectious Diseases, Metabolism, Nephrology, Neurology, Rheumatology, Pulmonology, Social Pediatrics, Newborn, Critical Care Medicine, Ethics and Health Service Research), as well as relevant specialities such as Pediatric Surgery, Child and Adolescent Psychiatry, Pedodontics, Pediatric Nursing and Family Physicians.

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The "p" value defined as the limit of significance along with appropriate indicators of measurement error and uncertainty (confidence interval, etc.) should be specified. Statistical terms, abbreviations and symbols used in the article should be described, and the software used should be defined.

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A Step in the Quest for Knowledge and Meaning: The Impact of Earthquakes on Health

Dear Readers,

We have prepared this special issue with the aim of commemorating the memory of those lost in a monumental tragedy and reflecting our pursuit of knowledge to better cope with similar disasters in the future. The devastating force of an earthquake affects not only infrastructures but also the healthcare systems of societies and the lives of individuals. This issue strives to provide an in-depth exploration of the health implications of earthquakes.
Science and healthcare play a crucial role in rebuilding and healing societies in the aftermath of such natural calamities. Humanity must draw lessons from every disaster and apply these lessons to future emergencies. This issue not only analyzes the impacts of earthquakes on healthcare services but also delves into ways of being better prepared for such occurrences.
The articles we include address various aspects of the topic, encompassing the healthcare system, emergency response, trauma management, psychosocial support, and rehabilitation. We believe the scientific studies featured in this issue possess the potential not only to shape the present but also to shape the future.

However, we must not forget that this issue is not solely a scientific exploration but also a tribute to the lives lost. We extend our gratitude to all researchers and authors who have contributed to the creation of this issue.

In this issue you will find the opportunity to read article about childhood immune thrombocytopenia and autism spectrum disorder and a case report with neonatal purpura fulminans.

We hope that this publication will showcase the power of sharing knowledge and fostering societal unity, while shedding light on our preparedness for similar calamities in the future.

Sincerely,
Ahmet Keskinoğlu

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Review

Infections After the Earthquake Disaster

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ABSTRACT

Earthquakes are among the most frequent natural disasters, responsible for approximately 1.87 million deaths in the 20th century. A magnitude-7.8 earthquake hit southeastern Turkey and parts of Syria in the early morning of February 6th, 2023. Earthquakes damage hospitals and healthcare facilities and lead to reduced emergency capacity. Such situations worsen the physical and mental health conditions of injured individuals. The incidence of infections due to injuries/trauma, water and foodborne infections, and acute respiratory infections were reported. Herein, we reviewed the infections among susceptible individuals, which may more easily develop in this area.

Keywords: Disasters, earthquake, infectious diseases

Introduction

Earthquakes are among the most frequent natural disasters, responsible for approximately 1.87 million deaths in the 20th century (1). Earthquakes occur with different frequencies around the world. Turkey is located on the Anatolian plate, where major earthquakes have occurred throughout history. From the 1900s to the present, 20 earthquakes with a magnitude of 7 have occurred, and unfortunately, Turkey is one of the countries most affected by earthquakes. A magnitude-7.8 earthquake hit southeastern Turkey and parts of Syria in the early morning of February 6th, 2023. The earthquake was followed by another 7.5 magnitude earthquake approximately 9 hours later, with more than 200 aftershocks causing at least 50,000 people to lose their lives, with thousands more injured.

Developing countries are more vulnerable to disasters because of their lack of resources, infrastructure, and disaster preparedness systems. Such devastating earthquakes have serious health, social and economic consequences. In the acute period after the earthquake, deaths are seen as a result of the collapse of the buildings where people live, and the traumas experienced. In the post-earthquake period, various infections may develop, and the earthquake survivors may be lost due to these infections. Stress from earthquakes and trauma, lack of hygiene, and unsuitable environmental conditions pave the way for infections. As a result of damage to infrastructure services such as electricity, water, and sewage systems, people's inability to access sufficient and clean drinking water and contamination from sewage systems to drinking water (fecal contamination), especially water and foodborne infections can occur. People who live in affected areas are usually forced to change their lifestyles, and sheltering the people affected by the earthquake in crowded camps also poses the risk of infections developing. Earthquakes damage hospitals and healthcare facilities and lead to reduced emergency capacity. Such situations worsen the physical and mental health conditions of the injured individuals. The post-earthquake period can be divided into three phases in terms of the development of infections (2):

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• **Phase 1 (0-4 days):** Treatment of injuries, skin and soft tissue infections secondary to trauma

• **Phase 2 (4 days-4 weeks):** Infections caused by collective life in the camp areas, contagious diseases

• Respiratory tract infections, droplet-borne infections.

• Foodborne and/or waterborne infections

• **Phase 3 (> four weeks):** Infections with long incubation periods, latent infections,

Post-earthquake infections and/or epidemics usually occur 4-30 days after an earthquake. The incidence of infectious diseases has been reported to increase after destructive earthquakes worldwide. Post-earthquake infections and/or epidemics can develop due to the displacement of large numbers of people, the overcrowding of communal living areas, a decrease in clean water resources and/or inadequate hygiene practices, an excessive proliferation of vectors, malnutrition, and many more adverse conditions which arise depending on the magnitude of the earthquake, particularly in developing and/or undeveloped countries. Respiratory, gastrointestinal and skin infections are the most common infections detected in the post-earthquake period.

Infections due to Injuries/Traumas

Wound infections are common after crush injuries. Traumatic abrasions and lacerations may become infected due to contact with concrete, wood, metal, soil, or contaminated water. The longer the stay under the rubble is, the higher the possibility of developing crush syndrome and the greater the risk of exposure to pathogens become. The deterioration of skin integrity with injury, necrotic tissue, and protein-rich exudate from the wound lead to bacterial colonization and infections. In addition to these facilitating conditions, fasciotomies also increase the development of infections. The most common agents in wound infections are *Staphylococcus* spp. and *Streptococcus* spp. Gram-negative bacteria such as *Aeromonas, E. coli, Klebsiella*, *Pseudomonas*, anaerobic pathogens, and fungi are the most commonly detected pathogens.

Chen et al. (3) reported that 66.7% of the patients with crush syndrome became infected after 48 hours of admission and *Acinetobacter baumanii* and *Pseudomonas aeruginosa* were the most common bacterial isolates in the wound infections after the Wenchuan earthquake. Guner and Oncu (4) reported that 60.9% of those patients with crush syndrome had wound infections, and 15% developed sepsis. Infectious complications were reported in 75.7% of the patients with crush syndrome in another article, of which wound infections were the most common. Wound infections occurred in all patients undergoing fasciotomy (5). *Staphylococcus aureus*, *Escherichia coli, Enterococcus faecalis*, and *Enterobacter cloacae* were the most frequent pathogens isolated from pus or wounds during the initial stage of admission, while *Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Klebsiella pneumonia* were the most frequent pathogens during the middle and advanced stages of admission (5). Sepsis and wound infections were reported to be the most common infectious complications after the 1999 Marmara Earthquake (6). *Acinetobacter* spp., *Pseudomonas* spp. and *Staphylococcus* spp. were the most frequent microorganisms detected in the blood cultures of those patients with sepsis, while *Acinetobacter* spp., *Pseudomonas* spp., *Klebsiella* spp., and *Staphylococcus* spp. were the most common in wound infections. Bulut et al. (7) documented infections in 25.8% of hospitalized patients after the 1999 Marmara earthquake. Deep surgical infection was the most common infection (33%), and bacteremia occurred in 20% of cases. The most frequently isolated microorganisms were *Pseudomonas aeruginosa, Acinetobacter baumannii*, methicillin-resistant *Staphylococcus aureus*, and *Candida* spp.

Water and Foodborne Infections

Diarrhea outbreaks, Hepatitis A and E infections can develop particularly in developing countries. Diarrhea is the most important cause of death in the shelter camps where the survivors stay (8). The cause of diarrhea is usually due to the use of dirty water. Water contamination can be caused by sewage mixing or contamination during its transportation and/or storage. In addition, diarrhea outbreaks have been reported to occur due to the use of common water tanks or the pots and pans used in food preparation. A lack of hygiene products and contaminated food are the other leading factors (9). *Salmonella enterica* serotype Paratyphi A, *Vibrio cholerae,* and norovirus are the most common pathogens (9,10). In a study conducted after the 1999 Marmara earthquake, it was reported that diarrhea cases increased after the earthquake, and the most common cause was *Shigella* spp. (11). Following the 2005 earthquake in Pakistan, an estimated 42% increase in diarrheal infections was reported in an unplanned and poorly equipped refugee camp (12). Due to poor hygiene, over-crowding, a lack of potable water, and ineffective sanitation, an increase in diarrheas was reported in Iran after the 2003 earthquake (13). *V. cholerae* is highly endemic in countries with pre-existing poor water, sanitation, and sewage systems where disasters such as earthquakes,

floods, and tsunamis can exacerbate the risk of infection; however, microbiological laboratories are often absent or limited in these areas.

Leptospirosis can be transmitted through contact with contaminated water, food and soil containing contaminated urine (leptospires) from infected animals (e.g., rodents). Contamination occurs through the contact of damaged skin and mucous membranes with water, damp soil, or mud contaminated with rodent urine. Increased risk factors and outbreaks were reported after Typhoon Nali (14) in China and Taiwan in 2001.

Increases in hepatitis A and hepatitis E have also been reported after earthquakes, in the event of the collapse of the sewer system, or when there is a disturbance in the discharge of wastewater or difficulties in accessing clean drinking water. Clusters of hepatitis A and E cases were also described among a susceptible community in Banda Aceh (Indonesia) following the 2004 tsunami disaster (15). Sencan et al. (16) evaluated the HAV and HEV seroprevalence in children living in post-earthquake camps in Düzce, with hepatitis A and E seroprevalence found to be higher in disaster survivors in those who had more difficulty in reaching hygiene materials. Kaya et al. (17) reported high hepatitis A seroprevalence (64%), persisting for four years after the 1999 Düzce earthquake; however, hepatitis E was rare (0.3%).

Infections Associated with Overcrowding

Acute respiratory infections (ARIs) may be increased due to overcrowding, poor ventilation, and poor nutrition in crowded shelters, specifically in cold weather (18). A study conducted after the 2001 El Salvador earthquake showed that 30% of affected people experienced upper respiratory tract infection (19). In Iran, ARIs were found among 14% of the survivors after Bam earthquake in 2003 (13).

Influenza, SARS-CoV-2, Measles, Neisseria meningitidis infections, and tuberculosis are important infectious diseases which can more easily develop in overcrowded camp areas; therefore, vaccination plays a critical role in preventing these pathogens. Crowded conditions also increase the risk of scabies infestation due to a lack of hygiene, insufficient water consumption, and the shared use of beds.

Ethics

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Review

Earthquake Related Orthopedic Traumas

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ABSTRACT

Earthquakes are natural events which can cause serious injuries and deaths in the affected areas. Orthopedic injuries are also very common in these events. The orthopedic surgeon's role includes interventions such as the temporary or definitive treatment of fractures, debridement, amputation, and fasciotomy. In this review, open fractures, crush injuries, compartment syndrome, and patients with crush syndrome and fractures which develop without being under debris, which are frequently encountered by orthopedic surgeons after an earthquake, will be reviewed with case examples in light of the literature.

Keywords: Crush syndrome, compartment syndrome, crush injuries, earthquake

Introduction

Earthquakes are natural events which can cause serious injuries and deaths in the affected areas. Although branches such as emergency medicine, general surgery, nephrology, orthopedics and traumatology are among the most intensively focused on branches in earthquake regions in the early period after an earthquake, the patient density of all branches increases significantly after the acute period (1).

The role of orthopedics and traumatology in earthquake injuries is quite large. The biggest reason for this is that patients who develop cranial or solid organ pathology usually die while under the debris (2). The most common procedures performed by orthopedic surgeons include interventions such as the temporary or definitive treatment of fractures, debridement, amputation and fasciotomy.

When an orthopedic trauma is encountered, the patient should be evaluated in detail in terms of other traumas such as solid organ pathology, chest trauma and cranial trauma. In particular, patients rescued from under collapsed structures should be considered as having spinal injuries until proven otherwise, and their transport should be carried out with the assistance of cervical collars and spine boards (3). For this reason, patients must be evaluated in a multidisciplinary manner and treated based on prompt decisions.

The authors have experience working for two weeks starting from the 24th hour after an earthquake in emergency hospitals and trauma centers where patients were referred. They have played a role in both emergency and definitive treatments of earthquake-related orthopedic traumas. This article includes examples of the five main groups of patients, which have been grouped by the authors and their discussion with the literature on these examples is given.

Management of Open Fractures

Open fractures are common after earthquakes (4). Studies have shown that this rate is 22% (5). Open fractures may occur as a result of the broken ends of the soft tissue integrity, or they may occur due to external trauma. Since earthquake injuries are usually caused by external high-energy trauma, there is a high risk of contamination, and

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therefore all open fractures resulting from earthquakes should be considered contaminated.

Open fractures are orthopedic emergencies and their treatment should begin at the scene. First of all, neurovascular pathologies should be evaluated and the wound should be wrapped cleanly with a wet gauze soaked in saline. Then, if possible, the extremity should be stabilized. After this stage, the patient should be transferred to the hospital, the patient's wound should be washed in the emergency room, tetanus prophylaxis should be applied and antibiotic therapy should be started. Tetanus immunoglobulin should be added to the treatment if the injury is dirty, non-viable tissue is present, or 6 hours have passed since the injury (6). In open fractures, prophylactic antibiotics should be administered for 24-72 hours, depending on the type. The most widely used classification in open fractures is the Gustilo-Anderson classification (Table I). Since earthquake injuries are considered Type III, a triple combination of first-generation cephalosporin, aminoglycoside (3-5 mg/kg/day gentamicin), and penicillin (2 million IU IV every 4 hours or vancomycin/clindamycin) should be administered. Taking pictures of the wound is also very important in terms of documentation.

Due to the urgency, detailed imaging is not required in earthquake injuries, but it is useful to evaluate the fracture configuration, bone defect and foreign bodies with anteroposterior and lateral radiographs which can be taken quickly. Computed tomography may be useful for surgical planning in joint fractures. If the patient's vital signs are stable when the intervention in the emergency department is completed, the patient is transferred to the operating room for further orthopedic interventions.

The first procedure to be performed in the operating room is detailed debridement. Debridement should be performed systematically from the superficial to the deep. Areas of skin which do not have circulation should be removed, but border areas may be given a chance. All suspicious areas in the fascia should be removed. In muscle debridement, the decision is made according to color, consistency, contractility and bleeding capacity. Suspected muscle tissue should also be debrided (7). Tendons which do not require repair should be preserved as much as possible. At the end of the debridement, the tendons should be covered with soft tissue. Bone fragments which do not remain in contact with the periosteum should be excised. Bacterial contamination can be reduced by irrigation after debridement.

Table I. Gustilo-Anderson open-fracture classification

Type	Description
Type I	Clean wound <1 cm in diameter with simple fracture pattern and no skin crushing
Type II	A laceration >1 cm and <10 cm without significant soft tissue crushing. The wound bed may appear moderately contaminated
Type IIIa	Adequate soft tissue coverage of the fracture despite high energy trauma or extensive laceration or skin flaps
Type IIIb	Inadequate soft tissue coverage with periosteal stripping
Type IIIc	Any open fracture that is associated with a vascular injury that requires repair

Fixation should be planned after debridement. Fracture fixation is crucial for bone and soft tissue healing and the prevention of infection (8). The fixation method is decided on according to the type of fracture. Classification is best evaluated intraoperatively, as the extent of the soft tissue injury and the degree of contamination is best assessed during surgery (9).

Type I fractures can be treated as closed fractures. However, since earthquake injuries are considered contaminated, all open fractures should be considered Type III regardless of size (9). In type II and type III fractures, if the vital soft tissue remaining after debridement is large enough to close the implant, definitive fixation can be applied. Otherwise, temporary external fixation and, in appropriate cases, a vacuum-assisted wound closure device can be used. This device acts by both reducing edema and stimulating the formation of granulation tissue. Graft or flap surgery can be applied when it has been ensured that there is no infected or dead tissue in the wound in the following sessions.

One patient in our sample had a type II open distal tibia fracture. After debridement of the open fracture in the operating room, temporary fixation was made with an external fixator and preparations for definitive treatment were started (Figure 1).

Crush Extremity Injury

Crush injuries of the extremity are very common, as injuries which develop after an earthquake are usually very high-energy. Crush injuries are severe injuries. Severe extremity injury is a condition in which three of the four tissue components (bone, vessel, nerve, soft tissue) in the extremities are damaged (10). Although the approach to these injuries is very similar to the approach to open fractures, there are also differences in terms of the need for aggressive treatment.

Figure 1. A patient with type II open tibial fracture temporarily fixed with an external fixator

The Mangled Extremity Severity Score has been defined to determine whether acute amputation or extremity salvage interventions should be performed in patients with crush injuries of an extremity (11). In this scoring system, the mechanism of injury, the vascularity of the extremity, the patient's age, and the patient's hemodynamic status (systolic blood pressure) are included. According to this scoring, it is possible to decide whether to perform limb-salvage surgery or amputation. Considering the high energy of the injuries seen in earthquakes and the prolonged ischemic duration of the patients, the appropriate treatment method for the patients is usually amputation.

Another guiding scoring system for patients with crush injuries is the Limb Salvage Index scoring system (12). A more detailed evaluation can be achieved with this scoring system. Parameters such as artery, nerve, bone, skin, deep vein, and warm ischemia time are evaluated.

The treatment choice for such patients is amputation even in fully equipped trauma centers, as amputation is both therapeutic and life-saving in crush injuries which develop after earthquakes, considering the lack of monitoring and follow-up facilities, the deficiencies in supportive treatment, the need for a multidisciplinary approach and excessive patient loads. Considering that scoring systems and examinations cannot be carried out under appropriate conditions in large disasters such as earthquakes which affect many people, sometimes a decision to treat with a clinical sense may have to be taken. Studies have shown that 1.23% of earthquake-related injuries require amputation (13).

A patient in our sample was a young male patient who was freed from the debris in the 24th hour (Figure 2). The patient had no additional trauma, except for a crushed leg. The patient was conscious, but his cooperation was not complete. There was no sensation on the sole of the foot. Distal pulses were not palpable. Under the conditions at that time, the laboratory data of the patient could not be evaluated in the preoperative period. The patient underwent emergency below-knee amputation.

Compartment Syndrome

Compartment syndrome is the development of increased tissue pressure in a closed osteofascial compartment, preventing capillary blood flow, causing ischemia in muscle and nerve tissues, and the development of permanent loss of function. Neural and muscle ischemia becomes irreversible within 6-8 hours after intra-compartmental pressure increases.

Diagnosing compartment syndrome begins with suspicion. In the conscious patient, pain, numbness, tingling, especially with passive stretching, and the inability to receive distal pulses in the later stages of compartment

Figure 2. A patient with a crush injury to the leg

syndrome are observed. Obtaining distal pulses does not rule out compartment syndrome. Differential diagnoses with crush syndrome should be made in these patients. In crush syndrome, the energy of the trauma is higher and the ischemia time is longer.

Compartment syndrome should be suspected in the presence of stiff and painful extremities after the patient is freed from debris after an earthquake. Diagnostic methods via measuring the compartment pressure invasively are not usually possible in an earthquake zone under emergency conditions.

Treatment methods in the presence or suspicion of compartment syndrome vary according to timing. Fasciotomy within the first 8 hours is crucial for the prevention of permanent sequelae in patients with injury. However, it is thought that fasciotomy can be applied and be beneficial in patients admitted between 8-24 hours after trauma. It is thought that performing fasciotomy after 24 hours increases complications such as infection and does not prevent permanent sequelae (14).

One patient in our sample presented with an injury in his hand. His pain increased severely with passive stretching. A fasciotomy was performed on the patient, including the hand and forearm (Figure 3).

Unfortunately, it is not possible to prevent all problems in patients after fasciotomy. Fasciotomy is a common surgical procedure which can be performed after trauma related compartment syndrome and its complications are not uncommon. Good wound care in the fasciotomy area is essential. In cases of infection in the fasciotomy area, repeated debridements must be applied.

Despite all supportive treatments after fasciotomy, the amputation rate was seen to be 14.8% (15). Amputation should be performed in those patients who have undergone fasciotomy in the presence of established necrosis at the demarcation line despite appropriate wound care, or in cases where the metabolic picture progressively deteriorates.

Figure 3. A patient with compartment syndrome

Crush Syndrome

Crush syndrome is one of the most common injuries after an earthquake. However, crush syndrome and crush injury of the extremity are different conditions and should be separated from each other. Muscle destruction develops in the crushed extremity in crush syndrome. After the toxic metabolites formed are added to the circulation, a clinical spectrum leading to multi-organ failure, renal failure, electrolyte disorders and even death is observed. Metabolic disorders, prevention strategies and nephrological perspectives on crush syndrome will be discussed in other sections.

In disasters where the number of patients is very high, a multidisciplinary approach and close follow-up in crush syndrome are also difficult. It is known that up to 20% of patients die immediately after being pulled out of the debris (16). In patients with crush injuries, intravenous fluid should be given as soon as possible, and even if possible, before being pulled out of the debris.

Despite all treatment methods, the difficult point in making a decision in treatment is deciding whether to perform an amputation in crush injuries. One of the most difficult decisions for an orthopedist is to amputate the extremity. Orthopedic wound care, fasciotomy, and debridement may be sufficient under conditions where close monitoring can be achieved and ideal fluid-electrolyte treatment can be provided under normal conditions. However, in extraordinary disaster situations, patients may be lost because they cannot receive adequate fluid-electrolyte treatment. In such cases, amputation removes the source of toxic metabolites and becomes a life-saving intervention. One patient in our sample was a 16-year-old male patient, who was freed from the earthquake debris at the 48th hour. He was resuscitated and intubated due to the development of cardiac arrest immediately after arriving at the hospital after his first examination (Figure 4). There were no distal pulses in his extremity and the extremity was purple in color. The patient underwent an emergency transfemoral amputation. The patient was extubated on postoperative day 0 after supportive treatment after amputation and was referred for further treatment.

As seen in this example, it may be necessary to take aggressive treatment decisions in extraordinary disaster situations. Of course, it would be more appropriate to apply gradual treatment instead of making aggressive decisions in centers with adequate monitoring and multidisciplinary work opportunities. Sometimes, however, amputation is a life-saving surgical procedure.

Figure 4. A patient with crush injury to the right leg

Closed Fractures

Although injuries such as open fractures and compartment syndrome are the first to come to mind when earthquake-related orthopedic traumas are mentioned, non-crush injuries are also not uncommon. Those individuals who stand up or try to run during an earthquake may also be exposed to orthopedic traumas due to severe shaking.

The authors' observation is that hip fractures or distal radius fractures are common in elderly osteoporotic patients, while rotational ankle traumas and ankle fractures are common in younger patients. In patients with this type of fracture, the first intervention should be performed with splints in the first center, the extremity should be elevated if possible, and then, considering that definitive treatment cannot be performed in the earthquake zone, referral to a trauma center should be provided. In one example, it was seen that the surgical treatment of a 32-year-old female patient who received a trimalleolar fracture while trying to run during an earthquake was performed in the trauma center to which she was referred (Figure 5).

Ethics

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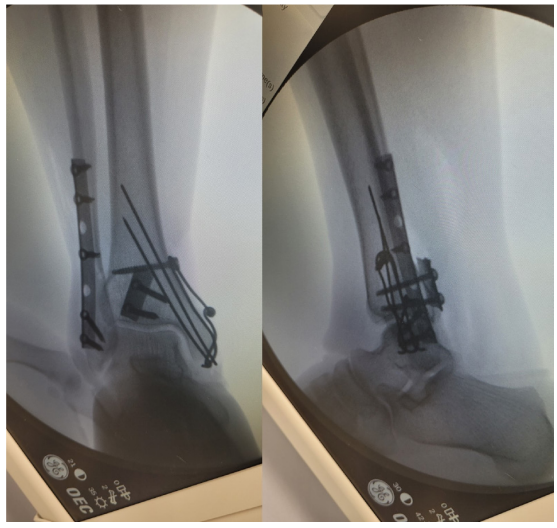

Figure 5. AP and lateral X-ray view of a trimalleolar fracture patient

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Review

The Devastating Turkey-Syria Earthquake from the Perspective of Pediatric Nephrology

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ABSTRACT

Kahramanmaraş was hit by two major earthquakes nine hours apart on February 6th, 2023, with magnitudes of 7.8 and 7.5 on the Richter scale, respectively. Ten other cities were also devastatingly affected by these earthquakes. More than 50 thousand people died in Turkey. The occurrence of two severe earthquakes on the same day in such a wide geographical area caused significant challenges. This disaster, with its devastating effects, focused attention on the significance of establishing a national and comprehensive emergency disaster plan prior to any disaster. Additionally, it highlighted the necessity of preparing a well-organized healthcare team capable of providing prompt and appropriate fluid replacement for pediatric patients in the early stages of a disaster. This is a crucial issue which must be addressed prior to major disasters. Another very important issue in this tragic disaster was the condition of chronically ill pediatric patients. Indeed, an emergency response is important not only for disaster victims, but also for those patients with chronic diseases in need of uninterrupted medical care. It is vital that individuals of all ages, as well as personnel from all sectors, receive the appropriate education, awareness, and knowledge on what actions to take, where to go, and where to gather in such situations.

Keywords: Earthquake, disasters, children, crush syndrome, crush injury

Introduction

Kahramanmaraş, which is located in the southeastern part of Turkey, was hit by two major earthquakes nine hours apart on February 6th, 2023, with magnitudes of 7.8 and 7.5 on the Richter scale, respectively. Ten other cities were also devastatingly affected by these earthquakes (1). As a result of these earthquakes, more than 50 thousand people died in Turkey, more than 8 thousand people in Syria lost their lives, and more than 122 thousand people were injured in total (2). The two major earthquakes caused damage to an area of approximately 350,000 km^2 and affected 14 million people, which represents 16% of Turkey's population. At the same time, severe winter conditions prevailed in the first days after the earthquake. The occurrence of two severe earthquakes on the same day in such a wide geographical area caused significant challenges. As in the 1999 Great Marmara earthquake, damaged roads and airports initially hindered rescue efforts, but urgently needed personnel and supplies were transported via ships and military helicopters (3).

To provide a clearer understanding of the situation, we wish to consider the case of a pediatric earthquake victim who was brought to a state hospital in the earthquake zone 18 hours after the event. A 16-year-old male patient presented to Adana City Hospital's Emergency Department

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18 hours after the earthquake. He had been rescued from the rubble by his family at the 14th hour and transported by ambulance with the assistance of the national professional medical team. It was noted that an unknown amount of isotonic saline had been administered to the patient during transport. His weight was 70 kg (50th-75th percentile), his height was 172 cm (25th-50th percentile), his blood pressure was 110/70 mmHg, and his body temperature was 36°C. Upon physical examination, diffuse hematoma, ecchymoses, edema and wound defect were observed in both distal lower extremities, extending up to the knees. Superficial abrasions were also present on the trunk and right arm. No fracture was detected.

The patient's hemogram showed hemoconcentration, with a hemoglobin level of 21 g/dL, white blood cell count of 36x10^3/µL and thrombocyte count of 218x10^3/µL. Biochemical analysis revealed acute kidney injury, with a urea level of 58 mg/dL, creatinine of 2.59 mg/dL, and uric acid of 8.8 mg/dL, as well as crush syndrome, with aspartate aminotransferase levels of 1,911 U/L, alanine aminotransferase levels of 455 U/L, creatine kinase (CK) levels of 142.560 U/L, CK-MB levels of 1,650 U/L, and LDH levels of 8,066 U/L. The patient also had an electrolyte imbalance, with a sodium level of 129 mmol/L, potassium levels of 4.8 mmol/L, calcium levels of 7.3 mg/dL, and phosphorus levels of 6.9 mg/dL. Coagulation parameters were normal. The patient's urine output was 0.08 mL/kg per hour, and the urine color was brown. In the emergency room, the patient received an isotonic saline bolus, followed by 2,500 cc/m^2 per day of ½ isotonic alkalized solution (50 mEq/L $NaHCO_3$). The patient's admission and follow-up laboratory data, along with his clinical course, are presented in Table I. This 16-year-old and about 1,000 other children in

Table I. The patient's admission and follow-up laboratory data and clinical progress

	Day 0 06.02	**Day 2 08.02**	**Day 3 09.02**	**Day 10 16.02**	**Day 14 20.02**	**Day 20 26.02**	**Day 37 16.03**	**Day 42 22.03**
Hemoglobin (g/dL)	21.2	18.2	11.8	6.7	8.1	10.4	10.4	9.7
Platelets (x10^3/µL)	218	158	113	101	113	218	483	368
WBC (x10^3/µL)	36	32.8	22.1	18.1	20	10.3	13.9	11.9
Urea (mg/dL)	49	110	154	148	120	74	46	39
Creatinine (mg/dL)	1.79	4.1	4.6	6.8	7.9	4.1	0.75	0.60
Uric acid (mg/dL)	8.8	12.2	8.9	6.4	8.7	5.9	6.6	6.5
Sodium (mmol/L)	129	124	130	136	125	131	138	137
Potassium(mmol/L)	4.8	8.2	6.2	4.4	3.8	3.8	4.06	4.6
Calcium (mg/dL)	7.3	6.9	8.5	8.1	7.5	7.9	10.5	9.8
Phosphorus (mg/dL)	6.5	11.4	9.3	3.3	4.2	4.4	4.4	4.5
Albumin (g/L)	3.3	2.3	2.4	2.0	2.8	2.8	2.9	3.1
AST (U/L)	1,911	1,740	1,854	158	41	28	20	23
ALT (U/L)	713	701	393	47	19	7	20	26
LDH (U/L)	1,650	6,704	4,096	594	363	376	255	191
CK (U/L)	142,560	166,950	120,010	2,180	880	580	228	-
CK-MB (U/L)	8,066	1,650	1,400	118	19	24	20	-
CRP (mg/L)	96	152	96	16	38	14	27	18
Urinalysis (HPF)	-	-	-	-	25E/20L	14E/13L	38E/7L	5E
Urine pr/cr (mg/mg)	-	-	-	-	2.69	2.29	0.96	0.52
UO (mL/kg per hour)	0.08	0.23	0.20	0.37	0.7	2.1	2.2	1.7
Intervention	Fasciotomy	PICU	Amp	Inpatient clinic	Stump repair			
Kidney replacement treatment	-	Yes (CRRT)	Yes (CRRT)	Yes (IHD)	Yes (IHD)	Yes (Last IHD)	Renal recovery	-

WBC: White blood cell, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, CK: Creatine kinase, UO: Urine output, HPF: High power-field, PICU: Pediatric intensive care unit, Amp: amputation, CRRT: Continuous renal replacement therapy, IHD: Intermittent hemodialysis

similar conditions were transported to hospitals both in the earthquake region and all over Turkey, with varying degrees of injury findings.

Earthquakes cause widespread human, material, economic and environmental losses (4). It has been reported that approximately 1 billion children under the age of 14 live in countries with high seismic risk (5). Child patients face additional difficulties during disasters. Losing their parents and other close relatives can make them feel incredibly lonely and disrupt their mental state. In normal times, children can easily receive medical care with the help of their parents, but in disasters, they may face challenges both psychologically and medically. During normal times, even parents may find it difficult to have their child's blood taken for diagnostic purposes, while in this catastrophic period, it may be necessary to obtain the children's consent to amputate their limbs in order to save their life.

In the 1988 Armenian earthquake, dubbed the "kidney disaster", approximately 600 victims who were rescued alive from the rubble developed acute kidney injury (6). In this review, the Gölcük earthquake and other disasters in our country are also extensively mentioned (7). In the most recent earthquake in Turkey, in addition to the devastating consequences of the earthquake, in the first month following the earthquake, heavy rains caused dozens of fatalities in three earthquake-stricken cities due to flood disasters.

It was seen that the majority of the patients who came in the first hours following the earthquake came by their own means. This indicates that those patients arriving within the first few hours after the earthquake require significant surgical intervention and that professional medical team intervention is lacking or inadequate. These patients are typically removed from the rubble immediately and have fewer crush injuries than expected. Patients who do not have an IV line, who have not received fluid replacement, whose vital signs are unknown, and who do not have identity cards may be encountered. In the following hours and days, such patients are superseded by more severely crushed patients, those who have been removed from collapsed structures by professional teams, who have vascular access and whose fluids have been started. At this point, these patients require the rapid insertion of an HD catheter and intensive dialysis. However, this must be performed with limited equipment and staff, and in facilities which have been damaged by the earthquake (8). The Turkish Society of Pediatric Nephrology (TSPN) took responsibility from the early hours of the disaster in Kahramanmaraş located in southeastern Turkey on February 6th, 2023 and became a part of the effort with other stakeholders. Rapid communication was established with the disaster area. The Crush Syndrome Initial Guidelines for children (9) and another guideline for neonates were prepared in collaboration with the Turkish Neonatology Association (10). Needs such as pediatric nephrologists, dialysis machines, catheters, dialysis supplies and medications were determined and provided with the coordination of the Disaster and Emergency Management Presidency and Ministry of Health officials. Ten volunteer pediatric nephrologists served in shifts in the earthquake affected zone.

Due to the nature of this earthquake, patients were rescued from the debris even after 10 days. Interestingly, crush injuries were less common in those patients who were rescued after the 5th or 7th day. This is probably because these patients were not severely traumatized, and dehydration was less developed in the cold weather present at that time.

Another very important issue in this tragic disaster was the condition of chronically ill pediatric patients (11). Indeed, an emergency response was important not only for disaster victims, but also for those patients with chronic diseases in need of uninterrupted medical care. We referred these patients to centers outside of the earthquake zone because of damaged houses, and difficulties in accessing care delivery or medications, dialysis fluids, and equipment. Even if they are able to access care facilities, they may be unable to find the doctors and healthcare professionals with whom they had previously been in contact with. Furthermore, during these times of crisis, cuts in transportation, electricity, natural gas, or water, and perhaps most importantly, communication can impede planning and treatment efforts (12).

This disaster, with its devastating effects, revealed the significance of establishing a national and comprehensive emergency disaster plan prior to any disaster. Additionally, it highlighted the necessity of preparing a well-organized healthcare team capable of providing prompt and appropriate fluid replacement for pediatric patients in the early stages of a disaster. This is a crucial issue which must be addressed prior to any major disasters. It is vital that individuals of all ages, from young children to the elderly, as well as personnel from all sectors, receive the appropriate education, awareness, and knowledge on what actions to take, where to go, and where to gather in such situations (13).

The International Society of Nephrology announced the theme for the 2023 World Kidney Day as "Kidney Health

for All" with the motto "Preparing for the unexpected, supporting the vulnerable!" (14). This message emphasizes the importance of including groups such as children in disaster preparedness plans. To this end, in order to increase awareness of earthquake preparedness and to manage earthquake-related medical and psychological problems, the İstanbul branch of the TSPN organized two meetings one week apart (15). Supporting medical teams during disasters is another important area which deserves much more attention. For this purpose, a meeting was held with the participation of the European Society for Paediatric Nephrology (ESPN) Disaster Taskforce, and online free registration support of the ESPN Congress was granted for pediatric nephrologists who worked in the EQ zone.

In disasters, it is crucial to have a comprehensive plan in place. Starting with the most vulnerable unit, the family, it is critical for each agency to have its own trauma team, management plan, and clearly defined allocation of responsibilities, including where to be and what to do in the event of an earthquake. It is also crucial to designate individuals responsible for record-keeping procedures, especially in healthcare settings (16). Collecting patient records is vital in order to correctly manage current and future disaster events. Therefore, a web-based data collection system was created by the TSPN, and its first results are being analyzed (17).

After such major disasters, many children are at risk of contracting infectious diseases such as diarrhea, pneumonia and scabies, and acute malnutrition, which can create a vicious cycle between the two. Some have lost limbs and will require lifelong physical rehabilitation, mental health care, as well as socioeconomic support. Others have lost their parents and homes, schools, and support systems, which can disrupt their daily lives and increase the risk of school dropout, mental health problems, child marriages, adolescent pregnancy, abuse, and violence in the long term. Additionally, earthquakes cause environmental pollution, including asbestos exposure from demolished older buildings, which is expected to have an impact especially on children (18).

Conclusion

In conclusion, disasters such as earthquakes are inevitable for some geographical areas and can occur unexpectedly, leaving vulnerable populations, such as children, particularly susceptible to the negative impacts of these events. Even if these children survive, they may experience early and long-term physical and social traumas. Therefore, it is crucial that medical professionals, including pediatricians, child psychiatrists, infectious disease specialists, and surgeons, are educated about the specific hazards these patients may face during disasters and they plan how and where they will work during such disasters.

Ethics

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Review

Psychiatric Effects of Earthquakes on Children and Adolescents

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ABSTRACT

Earthquakes have a negative impact on the mental health of children and adolescents. This article aimed to review common psychiatric reactions in children and adolescents after earthquakes, common psychiatric disorders such as acute stress disorder and post-traumatic stress disorder, grief, psychological first aid, child psychiatric consultation services during earthquakes, and preventive mental health approaches before earthquakes. In the first phase after an earthquake, children may experience normal acute stress reactions. Grief reactions due to loss of life may also be observed. Early psychological first aid is recommended for all child affected by an earthquake. The development of mental disorders such as post-traumatic stress disorder in children with severe and prolonged acute stress reactions and in high-risk populations warrants attention and early intervention. Post-traumatic stress disorder is a severe psychiatric disorder which can have long-term negative consequences. Appropriate use of child psychiatric inpatient services may be beneficial. Delirium is an urgent neuropsychiatric condition which requires careful management in this patient group. To reduce the impact of earthquakes on children's mental well-being, preventive mental health services should be strengthened.

Keywords: Earthquake, natural disaster, trauma, child mental health, consultation-liaison

Introduction

Psychological trauma is witnessing or learning that death, the threat of death, serious injury or threats to physical integrity have happened to you or to a loved one. Trauma occurs in three different ways: natural events (earthquakes, floods, fires, storms), man-made events (wars, abuse, murders), and accidental events. Disasters are traumatic events that cause physical and socioeconomic casualties. The consequences of disasters such as earthquakes can be acute and unpredictable (1). Major earthquakes can result in mass casualties. Children and adolescents in regions with active fault lines may be at risk of loss and trauma from earthquakes (2). In this context, it is important to have information about common psychiatric reactions in children and adolescents after earthquakes, their grief, required psychological first aid, any psychiatric disorders which may occur, and interventions.

Normal psychiatric reactions and psychiatric disorders after an earthquake

The psychological reactions of children and adolescents in the first few days after a natural disaster occur along a spectrum (3). Common symptoms include avoidance, altered perceptions of reality, re-experiencing, and separation anxiety in children who have experienced trauma (4). Patients may have problems with sleep and appetite, physical complaints, frequent crying, restlessness,

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irritability, and unresponsiveness. Other psychological symptoms include sadness, guilt, attention and memory problems, nightmares, loss of acquired skills (regression), and enuresis (5,6). The reactions which can occur in the first few days after a natural disaster are, "a normal response to an abnormal situation" and are referred to as "acute stress reactions" in the International Classification of Diseases. Acute stress reactions are a condition which often subside within two weeks. These are not considered to be a disorder or disease (4). Several psychiatric symptoms must be considered in trauma-related psychiatric diagnoses, such as repeated flashbacks of earthquake-related experiences, severe distress and avoidance of situations reminiscent of trauma, social isolation, incapacity to experience positive emotions, and extremely negative emotions such as sadness, guilt, and shame (6). In such cases, children should receive close supervision and support (7). Individual characteristics, family characteristics, social support, and trauma-specific characteristics all contribute to the severity and duration of symptoms (8). Differences in coping mechanisms may affect psychiatric outcomes (9). If the acute stress reactions are severe or prolonged, psychiatric disorders should be considered.

Psychiatric disorders commonly observed in children after earthquakes include acute stress disorder (ASD), post-traumatic stress disorder (PTSD), complicated grief reaction, depression, anxiety, and sleep disturbance (6-10). The most common post-earthquake condition in children is ASD (50.8%) (11). The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, defines ASD as a cluster of five symptoms: involuntary thoughts and memories, negative mood, dissociation symptoms, avoidance, and arousal due to actual or threatened death, serious injury, or sexual assault. Symptoms have been reported to last from three days to one month after the event (12). If the symptoms of ASD persist for more than one month, it is defined as a PTSD (13). PTSD is a serious mental health condition which can lead to loss of personal, family, and social functioning for many years (14). In the first two years after an earthquake, the rate of PTSD in children ranges from 19.2% to 24.4% (15). These percentages can vary depending on sample sizes, differences in study methodology, length of time after the event, and extent of destruction (6). In a study conducted during the Marmara earthquake, approximately 72% of children had moderate to severe symptoms of PTSD six months after a major earthquake (16). In another study, 74% of primary school children showed symptoms of PTSD in a survey performed approximately one year after the earthquake (17). PTSD in children and adolescents can lead to additional problems which impair functioning, such as alcohol and drug addiction, suicide, conduct disorder, risky sexual behavior, and difficulty concentrating (14). PTSD has been identified as a psychiatric diagnosis which should be approached most cautiously after disasters, as it is a predisposing factor for the development of depression (18). Supportive interviewing and use of psychopharmacological agents are recommended as interventions for PTSD (19).

There is a need for psychiatric screening, identification of at-risk groups, and effective use of intervention resources in mass disasters such as earthquakes (20). Vulnerable groups included children with pre-existing psychiatric disorders, those with special needs, and those who have experienced parental loss. In view of the negative consequences of further loss in vulnerable groups, early identification of the development of ASD and early intervention are important (21). According to a study from Japan, direct exposure to the earthquake, damage to the home, mode of evacuation after the earthquake, shelter conditions, loss, especially loss of the mother, and bereavement were strongly associated with post-earthquake psychiatric symptoms (22). A Greek study found that anxiety and PTSD were more common among children directly exposed to earthquakes than among those indirectly exposed to earthquakes. Female gender and younger age were found to be associated with PTSD. The severity of perceived danger at the time of the earthquake may predict PTSD, post-earthquake distress may predict depression, and female gender may predict anxiety disorders (20). A lack of mental health care for children with post-disaster psychological distress may be linked to negative long-term outcomes, according to a study which tracked trauma symptoms for ten years after disasters (23). After an earthquake in Armenia, adolescents who went untreated for post-earthquake symptoms were at risk of PTSD and depression, and short-term treatments (trauma-focused CBT) can prevent PTSD from developing (24). To conclude, we recommend that more attention should be paid to children with high risk factors for PTSD and other mental disorders and that those at risk should receive early intervention.

Psychological first aid after an earthquake

Psychological first aid is recommended as the first intervention for any earthquake-affected child (25). This means trying to give children a sense of security, peace, self-efficacy, attachment and hope (26). Ensuring their physical safety, providing them with nutritional support and keeping them in touch with relatives are some of the things which are recommended (27). When the safety and basic needs

of the children have been met, it is recommended that a relationship be established with them, as far as they will allow it. Children should be listened to with patience and sincerity; they should not be forced to have a conversation if they do not want to. The child's emotional expressions, such as silence, crying, anger, and self-blame, should be anticipated by those providing support (28). Playing and drawing can be used to share their feelings with young children (29). At the same time, it may be beneficial to provide physical contact to calm them and meet their nutritional and sleeping needs. Disasters can damage children's sense of control and trust. Questions such as, "*What food do you want to eat? What picture do you want to draw?*" or "*What do you want to do now?*" can be used to rebuild these feelings (30). The restoration of routines in the aftermath of a disaster is a critical intervention for the normalization of daily life (31). In this context, playgrounds and schools where communication between peers is established are of great importance (32). Reducing exposure to traumatizing stimuli, such as social media and television, is also recommended (33) (Figure 1).

Loss and grief in earthquakes

Earthquakes introduce many children to the concept of death. The loss of family members can lead to an increase in psychiatric problems, impairment in school and peer functioning, social withdrawal, behavioral problems, and physical symptoms. The important thing is to understand the normal grief reactions of children after loss and to recognize any pathological grief reactions. According to the model introduced by Kübler and Ros, grief goes through five stages: shock and denial, anger, bargaining, depression, and acceptance (34). Young children may find it difficult to understand concepts as abstract as the idea of death. They

Figure 1. The ''Do's and Don'ts'' in psychological first aid
**Created by the authors based on the literature*

may believe that the deceased might return, that they might be hurt, or that they might see the deceased and miss them. Older children may understand that death is both universal and irreversible. Explain to the bereaved child, in language that, they can understand that the person they lost will not return and that their body has gone (35). You can help children live through their grief without suppressing it by listening to them with patience and sincerity (18). Supporting the establishment of daily routines and giving children the opportunity to talk about their memories with their mother, father and siblings are some of the things that can be done. The child's pain may diminish over time as new relationships are formed and social life is normalized. Therefore, school and peer relationships should be supported and external support resources for children should be improved (36).

Complicated (pathological) grief comes to mind in cases where grief reactions are prolonged and complex situations are added (37). Research has shown that children who experience complicated grief after a disaster are at greater risk of developing depression, anxiety, and PTSD in the long term (38). Trauma-focused bereavement therapy may be useful in cases of complicated grief (39). There is evidence that trauma-focused cognitive behavioral therapy can help prevent PTSD and depression from developing (40). Major earthquakes can cause physical and environmental losses. All of these individual and social losses may be experienced as grief reactions in children. Therefore, by recognizing that losses are not confined to a single area, multi-dimensional support can be important in the event of devastating earthquakes (41).

Pediatric psychiatric consultations after the earthquake

Many children are admitted to pediatric wards after earthquakes (42). Considering that children who experienced disasters were healthy without mental disorders before the earthquake, psychological first aid should be provided to hospitalized children. Children with pre-earthquake mental disorders, special needs, physical losses from the earthquake, loss of family members, or a history of trauma should be referred to psychological support systems (43). Child psychiatric support may be useful when any psychiatric symptom is experienced intensely, stressors are high, or social support is low. If suicidal ideation, psychotic symptoms, disruptive behavior and/or substance abuse are observed, interventions should be prompt (7). In the early stages of a disaster, there is often a trend towards a reduction in the severity of psychiatric symptoms. Therefore, focus on psychoeducation in the consultation.

Close monitoring of symptoms with recommendations for behavior may be beneficial. It is recommended to be cautious about psychopharmacological interventions (44) (Figure 2). Delirium associated with head trauma and crush syndrome may be observed in children hospitalized after an earthquake (45). Delirium can complicate the differential diagnosis of pediatric clinical conditions due to its acute and fluctuating course (46,47). Impaired consciousness and orientation, distraction, sleep disturbances, hallucinations, irritability, inability to be comforted, loss of acquired skills, and decreased eye contact are the symptoms observed in children with delirium (19-47). The clinical situation can be improved by treating the underlying causes and controlling the pain and agitation (48). Lighting, providing a quiet environment, frequently reminding children of places, times, and people, regulating sleep hygiene, reducing immobility, reassuring children that they are safe, and keeping some of their favorite objects with them are some of the things which can be done. Psychopharmacological treatment includes antipsychotics. Opioids, anticholinergics, and benzodiazepines should be avoided. Melatonin may be used to regulate sleep problems (49). Research shows that within three months of discharge, 30% of children who experience delirium in the hospital present with symptoms of PTSD (50). Identifying delirium and intervening promptly to prevent further traumatization in children admitted to the hospital after trauma are important (47).

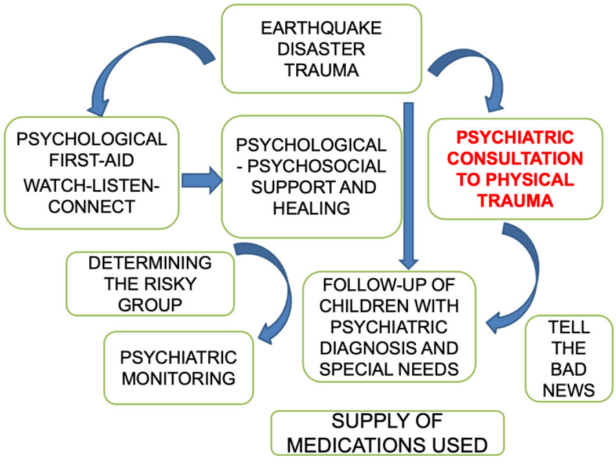

Figure 2. Post-traumatic psychological first aid and psychiatric consultation stages in trauma
**Created by the authors based on the literature*

Preventive mental health studies before earthquakes

Pre-earthquake programs to improve preventive mental health can be useful. Educating children about how natural systems work and how disasters occur is recommended prior to such disasters. Emergency plans for older children (e.g. earthquake drills at home and school) may be useful. When faced with predictable situations, children's coping skills may increase (51). In large-scale situations like disasters, it is important to recognize that social action plans can be provided (52). Following an earthquake in Haiti, studies have highlighted the need to address issues arising from the country's unstable environment, to strengthen families psychologically, and to prioritize child protection legislation to safeguard children's mental health. In addition, research has shown that unequal access to resources after a disaster can negatively affect children's mental well-being. Research on survivor dissatisfaction and inequalities in the recovery process is critical for understanding the mental health of children (17).

Conclusion

Severe earthquakes can affect several children and adolescents. Understanding common psychiatric symptoms and knowing how to provide psychological first aid can reduce the negative psychological impacts. Particular attention should be paid to ASD and PTSD and interventions should not be delayed patients with severe symtoms. The mourning processes of children and adolescents who have experienced loss should be emphasized. Therefore, support systems should be established. Efficient use of child psychiatric consultation systems in the post-earthquake phase in hospital inpatient units will benefit patients and the medical team. The most effective way to prevent mental illness after an earthquake is to protect children's mental health before disasters.

Ethics

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Original Article

The Evaluation of Children Admitted to Ege University Faculty of Medicine After an Earthquake in Terms of Health Services

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ABSTRACT

Aim: The most vulnerable victims of natural disasters are children. Health professionals have made great efforts to improve the health and psychosocial conditions of children from this region after the major earthquake disaster we experienced. This study aimed to evaluate those earthquake victims referred to our department of pediatrics in terms of health services and to share the results.

Materials and Methods: Children who were transferred to Ege University Faculty of Medicine, Department of Pediatrics after the earthquake were included in this study. It was recorded from which province these children came from, their age, gender, whether they were crushed or not, their physical health status, the duration of their stay in the hospital, their vaccination status, and whether there was any loss of parent or sibling.

Results: Five earthquake victims were referred, three from Hatay, one from Malatya, and one from Iskenderun. Of these children aged between 16 months and 16 years, 4 were boys, and 1 was a girl. In two of our patients, both lower extremities were amputated due to being trapped under rubble. The tetanus vaccine was administered to all children. It was discovered that 4 of our five patients hospitalized had lost a parent and/or sibling. The mean duration of stay in the hospital was 10.2 days.

Conclusion: It is crucial to determine earthquake survivors' needs during treatment, to work as multidisciplinary teams, and to make a follow-up plan for after discharge.

Keywords: Earthquake, pediatric, health service

Introduction

In our country, on February 6th, 2023, two major earthquakes of 7.8 and 7.5 occurred, respectively, in the Pazarcık and Elbistan districts of Kahramanmaraş (1). These earthquakes have been described as one of the biggest natural disasters for our country and the world. As a result of these earthquakes, more than 122 thousand people were injured in Turkey. As a result of the earthquakes, many people lost their families, homes, and jobs, but it is impossible to explain these losses with numbers alone.

The most vulnerable victims of natural disasters which affect many people are children. The Ministry of Family, Labour, and Social Services of the Republic of Turkey announced that it registered 1,915 unaccompanied children who were pulled out of the rubble after the earthquake on February 6th, 2023 (2). One thousand seven hundred eighty-eight of these children were handed over to their families, and 79 children were stated to be taken into institutional care (2).

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In earthquakes, it is crucial to give different priorities according to the needs of the children after first providing emergency support (removal from under the rubble, transport to the hospital, treatment, etc.) (3). Children may develop malnutrition and dehydration in a shorter time than adults. Infectious disorders which may emerge after an earthquake are more severe because their immune systems are not fully matured. Children's ability to withstand stress psychologically is less than that of adults. A child's development can be permanently affected if appropriate conditions are not provided (3). For the reasons mentioned above, doctors, nurses, psychologists, social workers, and other health workers should work together, and the essential support should be determined quickly for the earthquake survivors in hospital. Health professionals providing Primary Health Care have made great efforts to improve both the health and psychosocial conditions of children and families with children coming from the affected region after the major earthquake disaster we experienced. This study aimed to evaluate the earthquake victims referred to our pediatric department after their first treatment in the earthquake area in terms of health services and to share these results.

Materials and Methods

Children referred to Ege University Faculty of Medicine, Department of Pediatrics, for their treatment and follow-up after the earthquake on February 6th, 2023, were included in this study. It was recorded from which province these children came, their age, gender, whether they were crushed or not, their physical health status, their duration of stay in the hospital, vaccination status, and whether there was a loss of parents or siblings.

We aimed to provide health support for these urgently brought patients. In line with this goal, a social worker evaluated each hospitalized patient. After the children's identity information was verified, whether the accompanying persons were authorized to stay with the child was determined. According to the Ministry of Health's circular, children were reported on in writing to the Izmir Provincial Directorate of Family and Social Services on a daily basis. A psychological support action plan was prepared by making daily visits to the patients by pediatric, adolescent, and mental health physicians. It was aimed to determine the priority needs and to meet them quickly in the daily evaluation meetings attended by the physicians who organized the treatment of children, the social pediatricians, and social workers. For this purpose, the vaccination status of the children was checked, and after emergency tetanus vaccinations, it was determined whether there were any missing vaccinations in their vaccination schedules. In addition, situations such as clothing and financial support were also evaluated. Medical treatment reports which may be required during their stay in the hospital were prepared quickly (medicine, report on prosthetics due to limb loss. etc.). After the patients were re-evaluated before discharge, an outpatient treatment plan was explained, and priority patient appointments were made to outpatient clinics where they would be followed up. In addition, when the patients were discharged, they were handed over to their legally approved guardian via a signature. Support was provided for all our patients regarding a place to stay after discharge (in line with their requests).

Results

Five children referred to our department of pediatrics for hospitalization and treatment after the earthquake between the 6th and 13th of February, 2023 were included in this study. Table I shows the characteristics of these children, such as from which province they came, their age, gender, whether or not they were crushed, their physical health status, their duration of stay in the hospital, vaccination status, and whether there was any loss of parents or siblings.

Of the children who were aged 16 months to 16 years, 4 were boys, and 1 was a girl. Three children were referred from Hatay, one from Malatya, and one from Iskenderun. All of the children had been dug out of the rubble. The children's stay under the rubble ranged from 8 to 78 hours (mean 48 hours). Both lower extremities of two of our five patients were amputated due to compression by the rubble. When their vaccination statuses were examined, it was determined that 2 cases were fully vaccinated, and one case was missing those vaccinations which should have been given by the age of 4 years. However, the vaccination records of the other two cases could not be accessed from the national vaccination tracking system. All of the children were vaccinated for tetanus. In addition to our patients whose vaccines were missing, Diphtheria, Pertussis, Inactivated Polio, Measles, Rubella, and Mumps vaccines were also administered, and a vaccine schedule was prepared for our patients whose information could not be reached. The mean hospital duration of the patients was determined as being 10.2 days. It was discovered that 4 of our five patients had lost parents and/or siblings.

Table I. Characteristics of earthquake victim children

Patient number	**I**	**II**	**III**	**IV**	**V**
Age	Six years	Sixteen months	Six years	Sixteen years	Sixteen years
Gender	Boy	Boy	Boy	Boy	Girl
City	Hatay	Hatay	Malatya	Hatay	İskenderun
Trapped under the rubble	Yes	Yes	Yes	Yes	Yes
Time under the rubble	24 hours	53 hours	78 hours	8 hours	72 hours
Physical health condition	Two lower extremities amputated	Left arm trauma (fasciotomy)	Soft tissue trauma	Soft tissue trauma	Two lower extremities amputated
Immunization status	Incomplete immunization	Complete immunization	Complete immunization	Information not available	Information not available
Administered vaccines	MMR DTaP-IPV	Tetanus	Tetanus	Tetanus	Tetanus
Duration of stay in hospital	10 days	20 days	5 days	5 days	11 days
Loss of parent-sibling	No	Yes (mother and father)	Yes (mother and 2 siblings)	Yes (mother and father)	Yes (father and 1 sibling)

Discussion

The earthquake in Kahramanmaraş on February 6th, 2023, was reported as the biggest earthquake in our country. As with all natural disasters, there was much confusion regarding health services, particularly in the initial days following these earthquakes. While the rescue efforts for the people under the rubble continued, many reasons, such as the collapse of buildings which provided health care services, the fact that some of the health personnel working in that area were trapped under the rubble of the earthquake, the roads which the aid vehicles would use were blocked, and the lack of electricity and water made it challenging to provide health services. The earthquake victims removed from the rubble had to be transferred to different cities in order to continue their treatment after the emergency response. During this period, children, who are the biggest victims of natural disasters, needed additional support in comparison to adults. First, since their families were also under the rubble, it was necessary to identify the children, ensure they had companions, and determine their needs after discharge. For this reason, the children hospitalized in our hospital were evaluated with an approach via a collaboration of health professionals while their treatment was ongoing.

Problems such as identification and being unaccompanied during natural disasters are common (3). It was determined that four earthquake survivors in our hospital lost their parents and siblings. However, their identities and security were achieved since all of them and their legal companions were identified (with the permission of the İzmir Provincial Directorate of Family and Social Services). The Ministry of Family, Labour, and Social Services of the Republic of Türkiye announced that after the earthquakes, 79 children (who were not identified or had no adult to care for them) were taken into institutional care (2). However, this information stated in April, 2023 should be re-examined with updated numbers.

Head, neck, spine, thorax, abdominal injuries, extremity fractures, compartment syndrome, and crushes are the most common injuries in an earthquake (4). Extremity losses can also be experienced depending on the duration of being under the rubble and the severity of the damage. All of the children transferred to our hospital were removed from the rubble in an average of 48 hours. Compartment syndrome developed after left arm trauma and a fasciotomy was performed on one of our patients. In two of our patients, both lower extremities were amputated. Orthopedic-physical therapy physicians evaluated these patients, and the necessary procedures were initiated for prosthesis insertion. No signs of trauma were detected in the other three patients except for soft tissue trauma at different sites (Table I). Disaster situations such as earthquakes are critical because they can lead to missed vaccinations for children (5). In addition to the necessary emergency vaccinations after trauma, care should be taken not to interrupt the national vaccination program. Children and infants whose vaccination status is unknown should never be considered vaccinated, and a vaccination schedule should be made. After examining the vaccination status of the children in our study, the tetanus vaccine was administered to all of them.

Our patient with missing vaccines was given the missing vaccines, and those patients whose information could not be obtained were considered as if they had never been vaccinated, and an appropriate vaccination schedule was arranged. Post-discharge vaccination programs for these children were continued in the social pediatric outpatient clinic.

Psychological evaluation of children after disasters is critical. Children with parent/sibling loss should also be evaluated separately. The most common mental disorder which develops after trauma is post-traumatic stress disorder, followed by acute stress disorder, anxiety, phobic disorder, and sleep disorder (6). The cases in our study were examined daily by pediatrist, adolescent, and mental health physicians. This service continued after discharge after an appropriate psychological support action plan was prepared. It is known that there may be confusion regarding the health system during and immediately after natural disasters. As mentioned above, health professionals made great efforts to improve the health and psychosocial conditions of the children and families with children coming from the affected region after the major earthquake disaster we experienced. However, in cases of natural disasters, it is necessary to train health workers to be able to provide the support services to be given to children and their families.

Conclusion

As a result, it is essential to determine the needs of earthquake victims during treatment, to work as multidisciplinary teams, to have pediatricians at the head of the group, and to make follow-up plans for after discharge.

Ethics

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: M.T., F.K., Design: M.T., F.K., Data Collection or Processing: M.T., F.K., Analysis or Interpretation: M.T., F.K., Writing: M.T., F.K.

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Original Article

Characteristics of Pediatric Intensive Care Patients Following the 2020 İzmir Earthquake

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ABSTRACT

Aim: Unforeseeable disasters such as earthquakes can lead to significant catastrophes. Early and effective treatment methods are life-saving in reducing post-earthquake mortality and morbidity. The aim of this study was to evaluate the treatment and outcomes of patients with crush injuries in the Izmir earthquake.

Materials and Methods: Eight patients, 2 male, and 6 female were admitted to the intensive care unit. The medical records of these 8 crush injury patients were retrospectively reviewed.

Results: Eight children rescued from rubble were admitted to the pediatric intensive care unit, and one of them died. The median age of the patients was 148.5 (range, 35 to 210) months and the median PRISM score was 4 (interquartile range 0-31). The median duration of being trapped under the rubble was 23 (range: 4 to 92) hours.

Conclusion: Crush syndrome is a life-threatening event. The authors believe that early transportation and immediate intensive care therapy would have improved survival rates.

Keywords: Izmir earthquake, Crush syndrome, acute kidney failure

Introduction

Unforeseeable disasters such as earthquakes can lead to significant catastrophes. Early and effective treatment methods are life-saving in reducing post-earthquake mortality and morbidity. Immediately after earthquakes, the direct impact of trauma may result with disaster victims' deaths, while others may die under the rubble later, depending on the degree and location of their injuries, or be rescued and admitted to hospital. The first and crucial clinical findings in patients after earthquakes emerge at the disaster site. However, due to the chaos in the rubble area, there is limited comprehensive information about the type and characteristics of these findings in the literature. Therefore, knowledge about injuries and clinical findings in disaster areas is reached based on the clinical symptoms determined in hospital admissions (1,2). The most common complications observed after earthquakes include Crush syndrome, traumatic rhabdomyolysis, tissue injuries, multiple fractures, compartment syndrome developing after tissue damage, and acute kidney failure (3). The most

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affected areas are the lower extremities (74%), followed by the upper extremities (10%), and other body parts (9%) (3,4). Crush syndrome and traumatic rhabdomyolysis occur due to severe muscle injuries. The main mechanism of rhabdomyolysis is the stretching of the muscle sarcolemma under pressure. Increased permeability of the sarcolemma leads to the entry of sodium, calcium, and water into cells, activating proteolytic enzymes which cause membrane destruction. Elevated levels of potassium, phosphate, myoglobin, creatine kinase (CK), lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase and uric acid in the blood can lead to toxic and life-threatening complications (3). The effect of hypovolemia, combined with the activation of the renin-angiotensin and sympathetic nervous systems, exacerbates renal perfusion disorders. Simultaneously, increased myoglobin obstructs renal tubules, disrupting renal perfusion. Myoglobin reduction in the tubules releases free iron, catalyzing the formation of free radicals, further increasing ischemic damage. Acute tubular necrosis and acute kidney failure subsequently develop (3,4). Myoglobinuria obstructs renal tubules, leading to acute tubular necrosis and, consequently, acute renal failure in these patients (3-5). Hyperkalemia, hyperphosphatemia, hypocalcemia, myoglobinuria, and metabolic acidosis can occur within hours in this group of patients. Therefore, prompt initiation of appropriate fluid resuscitation is crucial (3,4). Compartment syndrome disrupts tissue circulation due to increased intra-tissue pressure caused by trauma or edema. Impaired blood supply leads to ischemia and edema, and without early intervention, tissue necrosis develops. Metabolic acidosis and myoglobinuria resulting from muscle tissue breakdown lead to kidney failure. Early recognition of compartment development in tissue areas and performing fasciotomy can prevent tissue losses (4,5). Electrolyte imbalances are widespread among crush victims of earthquakes. The aim of this study was to evaluate the changes in sodium, calcium, and phosphorus ions, renal function tests, and muscle enzymes in pediatric patients rescued from under rubble and admitted to the pediatric intensive care unit due to crush syndrome after the 2020 Izmir earthquake.

Materials and Methods

Patients rescued from the rubble after the Izmir earthquake on October 30th, 2020, and followed up in our pediatric intensive care unit were retrospectively reviewed. The patients' demographic information (age and gender), methods of presentation to the emergency department after the earthquake (outpatient/ambulance service), requested laboratory and imaging tests, administered treatments, consultations requested, and intensive care outcomes were analyzed. Cases resulting in acute kidney failure due to ischemia in crushed muscles and released products were defined as "crush syndrome". The condition of elevated serum muscle enzymes due to muscle necrosis and the release of intracellular muscle components was defined as "rhabdomyolysis". Cases with increased compartment intra-pressure requiring fasciotomy due to reduced tissue perfusion were defined as "acute compartment syndrome" (6-8).

Statistical Analysis

The Statistical Package for the Social Sciences version 22.0 package program was used for data analysis. Numbers and percentages are specified as descriptive statistical data (mean, standard deviation, minimum, maximum, median). Minimum and maximum values are specified as categorical variables, and mean values are given for numerical variables.

Results

On Friday, October 30th, 2020, at 14:51 local time, a severe shallow earthquake with a magnitude of Mw 6.6 occurred with its epicenter in the Aegean Sea (Seferihisar). This earthquake caused casualties and property losses, particularly in the districts of Bayraklı, Bornova, Buca, Kemalpaşa, and Menderes in Izmir, due to strong ground shaking and building damage (9). The earthquake resulted in the deaths of 116 people and injuries to hundreds. Eight children rescued from under rubble were admitted to the pediatric intensive care unit, and one of them died. Out of the 8 patients, 2 were male, and 6 were female. The median age of the patients was 148.5 (range: 35 to 210) months and the median PRISM score was 4 (Interquartile range 0-31). The median duration of being trapped under the rubble was 23 (range: 4 to 92) hours, the median length of stay in the intensive care unit was 28 (range: 20 to 160) hours and the median hospitalization duration was 97 (range: 12 to 528) hours. The first patient rescued after 4 hours had severe head trauma and passed away at the 30th hour of hospitalization. The demographic characteristics of the patients are presented in Table I.

Upon initial admission, complete blood counts, kidney and liver function tests, blood gases, and urine analyses were performed for all patients. As they had been trapped under the rubble for an extended period, fluid resuscitation with normal saline was administered at the disaster site, and no cases of hypoglycemia were observed. Fluid volume was adjusted for all patients based on age, weight, severity

Table I. Demographic characteristics of the patients

Patients (n)	Male/ Female	Duration under the wash (hours)	Stay in the intensive care unit (hours)	Hospitalization duration (hours)	PRISM score	Expected death rate (%)	Injured limb	Result
1	F	92	54	47	6	2.8	-	Discharged
2	M	11	160	528	14	13.2	Left and right lower extremities	Discharged
3	F	58	24	84	0	0.8	Left and right lower extremities	Discharged
4	F	4	30	30	31	83.7	Head	Ex
5	F	16	96	456	2	1.3	Left and right lower extremities	Discharged
6	F	65	26	110	2	1.3	Head	Discharged
7	F	23	20	264	0	0.8	Left lower extremities	Discharged
8	M	23	22	12	6	2.8	Left lower extremities	Discharged

of trauma, urine output, and physical examination findings, and sodium bicarbonate (30-50 mEq/L) in 0.45% NaCl with 5% dextrose (1/2 NS) was administered. Two patients underwent fasciotomy due to compartment syndrome. One of them was an 11-year-old male patient rescued 160 hours after the earthquake. Due to crush syndrome and compartment syndrome in the bilateral lower extremities, fasciotomy procedures were performed on both thighs and calves, superficial and deep posterior compartments were released. This closely monitored patient with crush syndrome and rhabdomyolysis had the highest CK level of 301.997 U/L, myoglobin level of 42.275 ng/mL, and creatinine level of 1.07 mg/dL. Mannitol at a dose of 0.5 g/kg was administered to increase urine output. The patient did not develop kidney failure and did not require dialysis. The fasciotomies performed for compartment syndrome were closed on the fifth day. The other patient was a 16-year-old female who was rescued from the rubble 96 hours after the earthquake. Fasciotomies were performed on both calves with two incisions each due to injuries in the lower extremities. A drop foot developed on the right-side during follow-up, and physical therapy was initiated. The fasciotomies were closed on the fourth day. A 17-year-old female patient was rescued from the rubble in the fourth hour after the earthquake. She was intubated, had a Glasgow Coma scale score of 3, and bilateral fixed dilated pupils. Despite aggressive treatment, the patient died at the 30th hour of hospitalization. Except for the patient who died, 7 patients did not require respiratory support. None of our patients in the pediatric intensive care unit developed kidney failure, electrolyte imbalances (hyperphosphatemia, hyperkalemia), or required dialysis. The intensive care admission and discharge kidney function test results and CK values of the patients are presented in Table II.

Discussion

Between 1998-2023, earthquakes caused nearly 850,000 deaths globally, more than half of all deaths related to natural disasters. More than 130 million people were affected by earthquakes during this time period, meaning they were injured, made homeless, displaced or evacuated during the emergency phase of the disaster. It takes years to eliminate the physical, psychological and economic effects which occur after an earthquake.

At 14:51 on October 30th, a magnitude 6.6 earthquakes in Izmir caused 116 deaths. The relatively low number of collapsed buildings during the earthquake and the rapid rescue efforts resulted in less development of kidney failure in the patients.

The locations and types of injuries observed after earthquakes vary depending on the countries' building characteristics. Following the 2005 Pakistan earthquake, superficial injuries such as lacerations and contusions were common, followed by orthopedic extremity injuries, head injuries, and chest injuries (5). In the 2011 Van earthquake, 95% of the disaster victims presented to the hospital with

Table II. Laboratory parameters of our patients

Patient	Hospital admission day				Before discharged			
	Urea (mg/dL)	Creatinine (mg/dL)	Creatine kinase (U/L)	Myoglobin (ng/mL)	Urea (mg/dL)	Creatinine (mg/dL)	Creatine kinase (U/L)	Myoglobin (ng/mL)
1	57	0.43	755	26	20	0.2	183	<21
2	40	1.07	43.597	30.000	47	0.33	301.000	8.344
3	37	0.57	1.781	41	17	0.55	364	<21
4	24	1.12	557	6.349	36	1.25	9.282	5.544
5	24	0.73	2.841	6.281	12	0.34	3.406	158
6	59	0.42	383	107	16	0.28	312	<21
7	34	0.70	14.034	1.393	17	0.47	10.590	218
8	52	0.61	10.917	2.464	15	0.4	9.730	278

soft tissue injuries (6). During the Marmara earthquake, the most affected area in the group of patients with crush syndrome was the extremities, with the lower extremities being more traumatized. The lower extremities contain larger muscle groups, leading to more rhabdomyolysis and a higher incidence of acute kidney injury. In the Marmara earthquake, 17.480 people died, and 43.950 were injured. Among 5.302 hospitalized patients diagnosed with crush syndrome and rhabdomyolysis, 639 had acute kidney failure, and 477 of them received dialysis. Crush syndrome resulting from upper extremity injuries generally had a milder course (10).

The İzmir earthquake had a magnitude of 6.6 and lasted approximately 16 seconds. The earthquake was felt throughout Western Anatolia, especially in the provinces of İzmir, Muğla, and Aydın. According to the Disaster and Emergency Management Authority, 116 people died, and 1,034 were injured (4). Many buildings collapsed or suffered severe damage in the Bayraklı and Bornova districts of Izmir, where the highest number of casualties and injuries occurred. Since our hospital is located in this region, all pediatric patients were admitted to the intensive care unit. Most of the presenting patients had non-life-threatening injuries. The relatively low number of pediatric patients trapped under the rubble was due to the earthquake occurring during daytime hours. The earthquake happened during regular working hours, with all clinics in our hospital working at full capacity, leading to a lower number of pediatric patients in need of immediate medical attention, and most of them had non-life-threatening injuries. Therefore, there were no issues in providing initial intervention procedures.

Among our patient population, 2 patients underwent fasciotomy procedures, and one of them was diagnosed Crush syndrome and received medical treatment. Crush syndrome is a systemic condition which arises as a result of trauma-induced rhabdomyolysis, leading to numerous medical and surgical complications. After earthquakes, there is a risk of crush syndrome and acute kidney failure in all patients with mild or severe muscle injuries. To prevent this, adequate hydration and the administration of alkaline fluids are essential. In our intensive care unit, which treated the most severe crush syndrome patients, none of our patients developed kidney failure or required dialysis. The use of mannitol to prevent acute kidney damage in crush injuries is controversial. It may or may not be beneficial in patients with traumatic rhabdomyolysis, or it may have the potential to cause harm. If the patient's urine output is sufficient (20 mL/h), mannitol can be administered. Studies have shown that in non-oliguric patients with traumatic rhabdomyolysis, close monitoring can prevent acute tubular necrosis and subsequent renal injury. In addition, mannitol may be useful in reducing edema in muscles and treating compartment syndrome (11,12).

Study Limitations

The retrospective nature and limited number of patients are the limitations of this study.

Conclusion

In conclusion, in earthquakes where the number of collapsed buildings and affected people is low, it is seen that patients are easier to manage both in the earthquake zone and in hospitals. With the 2023 Turkey-Syria earthquake, we,

unfortunately, experienced how devastating and terrible the consequences the opposite situations can cause. Although mortality and morbidity rates can be reduced with good planning and organization, it should always be a priority to take long-term measures to reduce mortality in natural disasters which we cannot prevent.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ege University Faculty of Medicine Medical Research Ethics Committee (approval no: 21-4T/52, date: 07.04.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.E.T., P.Y.Ö., G.K., İ.E., B.K., Concept: E.E.T., B.K., Design: P.Y.Ö., Data Collections or Processing: G.K., Analysis or Interpretation: İ.E., Literature Search: E.E.T., İ.E., Writing: E.E.T.

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Original Article

Disaster Consequences: Wish Hadn't Happened

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ABSTRACT

Aim: Natural disaster related injuries result in deaths and disabilities such as from a major earthquake. The object of this case series study was to determine the demographic characteristics, injuries, and clinical outcomes of victims admitted to a General Pediatrics Unit within the first weeks after an earthquake.

Materials and Methods: This was a retrospective case series study carried out on Kahramanmaraş earthquake victims in a tertiary medical faculty in İzmir from February 13th to March 29th, 2023.

Results: Of the followed up 9 earthquake survivors, their mean age was 3.8 years. All of the victims were transferred from other earthquake affected provinces to İzmir. In all, 9 of the cases were admitted to the emergency services of the disasters area hospital and 5 (55.5%) of the 9 cases were rescued from under rubble. For all age groups who were extracted from under the rubble, the extremities were most injured (44.5%). All survivors trapped under the rubble needed fluid therapy, renal support treatment (hemodialysis), and 2 cases required amputation.

Conclusion: The description of the demographic characteristics and clinical outcomes of earthquake victims is important in order to determine medical amelioration and rehabilitation services for future disasters.

Keywords: Earthquake, children, traumatic rhabdomyolysis

Introduction

On the 6th of February, 2023, known as one of the greatest disasters of the century, several series of massive earthquakes struck south-eastern Turkey including 11 provinces near the border with the Syrian Arab Republic. An earthquake of 7.7 magnitude struck and hundreds of aftershocks caused significant destruction at 04:17 local time with its epicenter located in the Pazarcık district in Kahramanmaraş province (Figure 1). Roughly 15 million people who lived in these areas and around 4.6 million children experienced the highest magnitude earthquake recorded and more than 13,000 aftershocks occurred, destroying hundreds of buildings, including schools. The earthquake devastated this area a week before the beginning of the second period of the school year, and consequently, all schools were closed for weeks in Turkey. Unfortunately, the victims suffered not only physical, but also significant psychological damage. With the addition of limb and organ losses to this situation, pain grew exponentially and it deeply affected the entire community.

According to Disaster and Emergency Management Presidency, more than 45,000 people were reported to have been killed across Turkey as of the 6th of March, more than 115,000 people were injured, and 9.1 million people were affected by the earthquakes (1). Although there is no certain data regarding children, exposure to earthquakes can cause serious health problems, especially in early childhood. The lack of personnel/death of staff during

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Figure 1. The provinces affected by the earthquake (World Health Organization)

earthquakes and damage to medical infrastructure may lead to an increase in the loss of life and injuries caused by earthquakes. Unfortunately, the injuries presenting needed intensive curative medical and surgical care putting strain on both the local and regional medical services for all territories (2,3). As part of this need, physicians from all over Turkey were sent to the affected regions. Patients from the affected regions were also referred to various clinics outside of the affected regions. The purpose of this case series study was to describe the characteristics of the victims' demographic features, injuries, and their clinical outcomes, for those cases who were referred from the earthquake zone to the Ege University Faculty of Medicine Children's Hospital General Pediatric Clinic within the first week after the earthquakes. To the best of our knowledge, this article is one of the first to investigate in depth the medical support and harm/loss profiles of pediatrics victims who were provided with medical and psychological support during the posttraumatic period in the Kahramanmaraş/Turkey earthquake. This case study could contribute to the recovery policies, and so help in improving and developing preparedness for future disasters such as earthquakes.

Materials and Methods

Participants and Data Collection

After the Kahramanmaraş earthquake, in the early hours of the disaster, a contingency plan was immediately launched involving a rescue operation by national and international medical institutions. A number of injured people and children were transferred to other hospitals such as Ege University, Childrens' Hospital in the first weeks after the earthquake due to the absence of medical equipment and support in the earthquake zone in the first days after the earthquake.

This study retrospectively investigated the clinical records of the admitted patients to the General Pediatric Ward from the earthquake area. The participants were evaluated as earthquake victims by using data between February and March, 2023 from Kahramanmaraş province and the southeastern Anatolia region of Turkey. The participants' parents and family members provided various information related to their demographic and social data. In addition, detailed information from other hospitals about the management of medical relief work was also obtained via interviews with medical professionals and medical rescue teams. The clinical records of 9 pediatric earthquake victims, who were admitted to our ward based on their medical records database, including demographic data, diagnoses, injury profiles, complaints, etc., were collected by a physician in the general pediatric unit. The diagnoses for patients with injuries or diseases were based on the final diagnosis such as the occurrence of any post-earthquake symptoms experienced by the participants, and systemic dysfunctions and anxieties according to the attending general pediatric unit physician. In the light of this diagnosis and the preliminary diagnoses, the patients were treated in the pediatric clinic, the pediatric sub-disciplines, and other departments for their critical follow-up, and a prosthesis process for amputee patients was started.

Ethical Considerations

This study adhered to the tenets of the Declaration of Helsinki and was approved by the Ege University Faculty of Medicine Clinical Research Ethics Committee (approval no: 23-6.1T/44, date: 06.07.2023).

Results

General Profile

The mean age of the hospitalized patients in the General Pediatrics Unit of Ege University Childrens' Hospital was 3.8 years. Of these, 6 (66.6%) were male. Due to this natural disaster situation with its transfer chain, the number of hospitalized patients reached a peak in the first week after the disaster. The admissions of the 9 patients is shown in the table which also shows their demographic data, reason for hospital admission, and injury diagnosis (Table I). During this period, only 9 patients were referred from the earthquake zone. Four of the patients presented with multiple injuries (44.4%), and the others with a single or no injury. Among the patients trapped under the rubble with multiple injuries, 3 patients with crush syndrome and rhabdomyolysis presented with acute renal injury and renal insufficiency. There were only four patients who

Table I. Demographic data, reason for hospital admission, and injury diagnosis of admitted patients with earthquake-related

	Patients				
	(Case 1) İ. M.	**(Case 2) S. Ö.**	**(Case 3) D. A.**	**(Case 4) H. Y. D.**	**(Case 5) A. T.**
Data					
Hospital stay interval	10/02/2023-21/02/2023	13/02/2023-05/03/2023	13/02/2023-24/02/2023	05/03/23-09/03/23	10/02/2023-11/02/2023
Date of birth	31/07/2016	07/10/2021	09/04/2006	27/04/2011	01/10/2021
Age	6 years	1 year 4 months	16 years	1 year 7 months	1 year 2 months
Gender	Male	Male	Female	Male	Male
Earthquake city	Adana	Hatay	Hatay	Kahramanmaraş	Kahramanmaraş
Pull from rubble time (hours)	Unknown	53 hours	Unknown	Unknown	2 hours
Length of hospital stay (day)	11	21 days	12 days	5 days	2
Reason for hospital Admission	Crush syndrome, acute renal injury, amputation	Crush syndrome and left ulnar artery injury?	Amputation of right knee left below knee, right thorax tube with pneumothorax, and liver contusion	Pneumonia	Victim observation
Physical examinatıon	Two-leg above-knee amputee	Left forearm with fasciotomy in splint	Amputation of right knee and left below knee	Tachypnea and bilateral rales on the lung	No major traumatic features
Surgical operation	Both legs were amputated above the knee (before admission)	Left forearm fasciotomy (before admission)	Amputation of right leg above knee, left below knee (before admission)	No	No
Final diagnosis	Past crush syndrome and amputation	Past crush syndrome and fasciotomy	Past pneumothorax, and amputations	Pneumonia, victim observation and discharge	Victim follow-up and discharge
	Patients				
	(Case 6) E. B.	**(Case 7) M. S.**	**(Case 8) M. M. G.**	**(Case 9) Y. G.**	
Data					
Hospital stay interval	10/02/2023-12/02/2023	12/02/2023-16/02/2023	11/02/23-16/02/2023	08/03/2023-13/03/2023	
Date of birth	01/03/2007	15/12/2022	14/07/2016	29/09/2017	
Age	1 year 7 months	2 months	6 years	5 months	
Gender	Female	Female	Male	Male	
Earthquake city	Hatay	Kahramanmaraş	Malatya	Hatay	
Pull from rubble time (hours)	10	Unknown	78	10	

Table I. Continued

	Patients			
	(Case 6) E. B.	**(Case 7) M. S.**	**(Case 8) M. M. G.**	**(Case 9) Y. G.**
Data				
Length of hospital Stay (day)	3	4	6	6
Reason for hospital Admission	Femur fracture, follow-up	Mild tachypnea	Rhabdomyolysis follow up	Pneumonia
Physical examinatıon	Hematoma, abrasion, ecchymosis on left leg with splint (visible parts)	Bilateral sibilant rhonchus and wheezing	5 cm incision in the forehead	Tachypnea and bilateral crepitant rales on the lungs
Surgical operation	No (Femur operation before admission)	No	Forehead area debridement and site repair	No
Final diagnosis	Left femur fracture	Bronchiolitis	Forehead area trauma, past rhabdomyolysis	Pneumonia, victim follow-up

were followed up for observations and clinical progress for respiratory problems such as pneumonia and bronchiolitis.

One of the most harrowing patients was an orphaned 6-year-old male patient who was trapped for unknown hours under the earthquake debris. Before transporting the child to our hospital, he was evaluated by physicians for general progress and injuries. His bilateral thigh was edematous and painful. Laboratory results revealed creatinine: 1.58 mg/dL, potassium: 6.11 mmol/L, serum pH: 7.35, bicarbonate: 16.8 mmol/L, lactic acid: 5.48 mmol/L and creatinine phosphokinase (CPK) of 25,700 U/L. Despite fluid and bicarbonate infusion, his renal function deteriorated, and his bilateral thighs became more tense resulting in a compulsory fasciotomy. He required 2 additional sessions of hemodialysis before complete resolution of the acute renal failure caused by traumatic rhabdomyolysis. By that time (24 h after hospital admission), the bilateral lower extremity was severely cold and cyanotic despite fasciotomy, so above-knee amputation was performed. He was transferred to our hospital's general pediatrics ward 5 days after admission to begin rehabilitation and administration of the general health follow-up with a stable cardiorespiratory state (SpO_2 of 98%, heart rate of 89 bpm, blood pressure of 96/62 mmHg and a respiratory rate of 18/min). On presentation, he was evaluated as having a Glasgow Coma Scale of 14 and showed a deeply depressed mood. Initially, the boy was evaluated by pediatric orthopedic surgeons for the first stage of damage control. Clinical examination revealed no pathological sign except two-leg above-knee amputation. Biochemical studies revealed aspartate amino transferase of 232 IU/L, alanine aminotransferase of 131 IU/L, and gamma-glutamyl transpeptidase of 10 IU/L, CPK: of 5,636 U/L, C-reactive protein of 1.6 mg/dL, creatinine of 0.4 mg/dL with normal urine output and urinary analysis. He was examined in the pediatric psychiatric department for trauma symptoms, which may be associated with long-term negative psychological changes in children experiencing disasters. General systemic disease screening and other necessary examinations were performed along with biochemical controls, as well as consultations for vaccinations and rehabilitation with social workers and the social pediatrics department. He was finally discharged 11 days later with a follow-up plan.

Discussion

Earthquakes are natural disasters characterized by strong terrestrial movements in a short period of time and they may cause destruction to health and the medical infrastructure. It was stated that 387 natural hazards and disasters occurred worldwide resulting in the loss of 30,704 lives affecting 185 million individuals in 2022 according to Emergency Event Database ''EM-DAT'', International Disaster Database. Earthquakes have injured more than 60 million people and approximately 400,000 have been killed during the last 30 years (4). Regrettably, our country is located in the Mediterranean-Alpine-Himalayan belt which produces at least one earthquake with a magnitude ranging from 5.0 to 6.0 every year. Turkey is one of the most earthquake prone countries in the world. In Turkey, on average, once every five years, a major earthquake occurs causing a loss of life and property damage on a large scale (5). On February 6th, 2023, two major earthquakes of magnitudes 7.7 and 7.6 with a 9-hour interval, and also a total of 11,020 aftershocks occurred on the Eastern

Anatolian Fault Line, violently shaking 11 provinces in the Eastern and Southeastern Anatolia regions. Pazarcık and Elbistan of Kahramanmaraş province were determined as being the worst affected districts of the earthquake (6).

The management of polytraumatized pediatric patients suffering from earthquakes needs to be handled via a multidisciplinary approach including pediatric and orthopedic surgeons with the aim of damage control. The first stage of treatment to prevent death is to control any bleeding, to reduce contamination, to implement renal replacement therapy, to provide a temporary fixation on extremities, to supply a fluid-electrolyte balance, and to consider any surgical requirements (i.e., debridement, fasciotomy, or amputation) (7,8). Several earthquake studies have mostly reported that fractures were a large share of injuries, followed by soft tissue injury, contusions and lacerations. In an adult study on the 2013 Lushan Earthquake in China conducted by Peng Kang et al. (9), fractures accounted for 41.5% of the injuries, soft tissue injuries accounted for 27.5%, and contusions and lacerations accounted for 25.0%. The lower extremities and pelvis have been determined to be the most frequently injured anatomic sites, followed by the body surface, head, and spine in other earthquake studies (10). In our study, the patients suffering from earthquake-related physical trauma showed higher incidences of orthopedic injuries, particularly extremity problems of the lower limbs and traumatic rhabdomyolysis resulting in amputations and renal injuries. The most often injured anatomic areas were the extremities, followed by the body surfaces, and head. After stabilizing life-threating conditions, the patients need to be evaluated with a systemic approach, with both physical and psychological support in order to improve their life conditions. Orphaned children should be consulted by a social worker and the social pediatrics department. Our patients were evaluated by multiple departments, pediatrics divisions, and other disciplines during their hospitalization.

Earthquake-related mortality and morbidities generally originate from multiple-traumas, multiple fractures, soft tissue injuries, and crush injuries caused mostly by building collapses for individuals with poor socioeconomic conditions, who live in poor quality structures. One of the most threatening events in major earthquakes is traumatic rhabdomyolysis, also known as crush syndrome, which leads to acute kidney injury and failure. The mechanism of this syndrome is characterized firstly by ischemia and the reperfusion of decompressed extremities. During compression and ischemia, an intracellular influx of calcium occurs due to low production of adenosine triphosphate causing muscles lysis (8). Traumatic rhabdomyolysis has been reported following several earthquakes from all over the world, including Turkey. In the Marmara earthquake in 1999, crush syndrome accounted for 33% among hospitalized patients (11). Another earthquake study reported 48.9% of survivors were trapped under rubble and were diagnosed with extremity crush injuries (12). In the present study, 3 patients (33.3%) were identified with crush syndrome and presented with renal injury.

Earthquake-related injuries are mostly influenced by the location and/or being awake or asleep. Due to the fact that the victims could not escape due to the building collapses, numerous people were trapped under the rubble in their homes during the earthquake at 04:17 local time. Due to the fact that children are vulnerable to trauma and their body mass is small, they are more likely to be affected by major traumas. Amputations are the most difficult decision regarding crush injuries despite their life-saving aspect (13). In this present study, the extremities were the most injured anatomic part and needed to be amputated in two patients.

Study Limitations

The present study had several limitations. Firstly, the case series were retrospective in nature and secondly, there could have been a lack of record keeping or incomplete record keeping among the parents or other family members.

Conclusion

Earthquakes are natural disasters with the potential of causing death and homelessness. On February 6th, 2023, a large number of people and children who had been trapped under rubble needed a thorough evaluation, and most of those pulled from under the rubble were unfortunately admitted to hospitals as deceased. It is not possible to predict where and when earthquakes will occur or their severity despite todays' technological improvements. In order to avoid unfavorable consequences during earthquakes and earthquake-related deaths and injuries, policies for preparedness, response, emergency response systems, and disaster loss reduction strategies should be planned and implemented by government institutions.

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Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Ege University Faculty of

Medicine Clinical Research Ethics Committee (approval no: 23-6.1T/44, date: 06.07.2023).

Informed Consent: Informed consent with verbal consent was taken from the participants' parents.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ş.G., B.E.D., B.A., Concept: Ş.G., B.E.D., Design: Ş.G., B.E.D., Data Collection or Processing: B.E.D., B.A., Analysis or Interpretation: Ş.G., B.E.D., Writing: Ş.G., B.E.D.

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Original Article

An Overview of a Pediatric Rehabilitation Clinic After the Kahramanmaraş Earthquakes

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ABSTRACT

Aim: This study aimed to reveal the characteristics of patients who were rehabilitated in a pediatric rehabilitation clinic after an earthquake disaster.

Materials and Methods: The records of earthquake victims who were affected by the earthquakes in Kahramanmaraş on February 6th, 2023 and hospitalized in our Pediatric Rehabilitation Clinic between February 6th and June 6th, 2023 were retrospectively reviewed. The patients' demographic data such as age, gender, the city they lived in, duration of stay under the rubble, presence of crush syndrome and dialysis needs, fasciotomy and hyperbaric oxygen therapy (HBOT) history, amputation status and levels, accompanying fracture, peripheral nerve damage, brain injury and the presence of spinal cord injury were noted.

Results: Of the 60 inpatients rehabilitated in our clinic, 31 (51.7%) were female and 29 (48.3%) were male. The mean age of the patients was 10 (±0.76) years. Twenty-two (36.7%) of the patients experienced the earthquakes in Hatay, 21 (35%) in Adıyaman, 13 (21.6%) in Kahramanmaraş and 4 (6.7%) in Gaziantep. The length of stay under the rubble of 50 patients was recorded, with a median of 12 (1-96) hours. Crush syndrome developed in 25 (41.6%) of the patients, and 14 (23.3%) of them needed dialysis. HBOT was applied to 10 (16.6%) children. Peripheral nerve damage was detected in 42 (70%) children by electro-neurophysiological or physical examination methods. The most commonly damaged nerve was the sciatic (16%). Thirty four (56.6%) patients underwent fasciotomy. There were fractures in a total of 13 (21.6%) children. Seven (11.6%) patients had amputations in various parts of the extremities. Five (8.3%) of the patients had varying degrees of traumatic brain injury. Spinal cord damage was not detected in any of our patients.

Conclusion: In the pediatric population, musculoskeletal injuries caused by earthquakes and their complications are very important in the development and realization of disaster rehabilitation strategies.

Keywords: Children, disaster, earthquake, pediatric rehabilitation, rehabilitation

Introduction

Geologically, Turkey lies on a fault line and is an earthquake prone zone. On February 6th, 2023, two major earthquakes occurred in Kahramanmaraş. These two earthquakes caused widespread damage and thousands of deaths or injuries in ten provinces in Turkiye.

Injuries are the most important cause of earthquake-related morbidity (1). Crush injuries are classic features of earthquakes and can develop into potentially fatal crush syndrome. Infections and conditions which can lead to amputation are also common. Fractures, head injuries, and peripheral nerve damage are common and all these conditions require rehabilitation. After the first and

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emergency interventions after this major disaster, many children and adults were treated with physical therapy and rehabilitation programs at various centers according to their needs.

Although there are several studies in the literature on earthquake survivors from various aspects, to the best of our knowledge, there was no study directly examining pediatric patients treated in a Pediatric Rehabilitation Clinic (2-5).

Since the number of clinics dedicated to pediatric rehabilitation is very few, in this study, we aimed to examine the characteristics of pediatric patients who were hospitalized for post-earthquake rehabilitation. With this work, physical medicine and rehabilitation specialists will be able to have information regarding which strategies they should follow in cases of similar disasters.

Materials and Methods

For this study, the records of all patients under the age of 18 who were hospitalized and rehabilitated in our Pediatric Rehabilitation Clinic were retrospectively reviewed. The information of the earthquake victims who were affected by the earthquakes in Kahramanmaraş on February 6th, 2023 and hospitalized in our clinic between February 6th and June 6th, 2023 were reviewed.

The patients' demographic data such as age, gender, the city they lived in, duration of stay under the rubble, crush syndrome and dialysis needs, fasciotomy and hyperbaric oxygen therapy (HBOT) history, amputation status and levels, accompanying fracture, peripheral nerve damage (with the results of electro-neuromyographic (ENMG) examinations), brain injury and the presence of spinal cord injury were noted. The characteristics of a few cases which we thought were special and which we had difficulties in managing were reviewed in more detail (such as a case with neuropathic pain (NP) and a high LANSS (Leeds Assessment of Neuropathic Symptoms and Sign) scale, a case with delayed fracture healing, cases requiring evaluation by hand surgery, and several cases with high kinesiophobia). The drugs used in pain control and the last ambulatory status of the patients were noted. This study was approved by the Ethics Committee of Ankara Etlik City Hospital (date: 20.06.2023, approval number: AEŞH-EK1-2023-265) before the study, and it was conducted in accordance with the rules of the Declaration of Helsinki.

Statistical Analysis

SPSS version 20.0 was used for statistical analysis. The conformity of the data to the normal distribution was examined using the Shapiro-Wilk test. Categorical values are presented as n (%), non-normally distributed numeric data are presented as median (minimum-maximum).

Results

Tables I and II show the characteristics of pediatric earthquake victims hospitalized in our clinic for rehabilitation.

Table I. Characteristics of pediatric earthquake victims-1

No	Gender	City	Hour*	Fasciotomy	Amputation	Fracture	Brain injury	Peripherial nerve injury	Drugs for pain control	Final ambulatuar status
1	G	H	36	-	Left transtibial	-	-	-	-	Indepent with prosthesis
2	B	H	16	Left thigh and cruris	-	-	-	Left sciatic and femoral	-	KAFO and one-person support
3	B	H	8	-	-	Right femur	-	Right median	-	One-person support
4	G	H	?	Left forearm and thigh	Left transmetatarsal	-	-	-	-	Sitting independently
5	G	A	7	Left thigh and bilaterally cruris	-	Left tibia	-	Left sciatic	-	AFO and walker
6	B	A	1	-	Right hip desarticulation	-	-	-	-	Sitting independently
7	B	A	80	-	-	Left 1st metacarp	-	Left radial	-	Independent
8	B	A	72	-	Right transhumeral	-	-	-	-	Independent

Table I. Continued

No	Gender	City	Hour*	Fasciotomy	Amputation	Fracture	Brain	Peripherial nerve injury	Drugs for pain control	Final ambulatuar status
9	B	H	9	Right tight and cruris	-	-	-	Right femoral	-	Independent
10	B	A	5	-	-	-	SDH	Left peroneal	-	Independent
11	G	A	72	Left cruris	-	-	-	Left peroneal	-	Afo
12	G	K	20	Left cruris	-	-	-	-	-	Independent
13	B	H	9	Right forearm	-	-	-	Right median, ulnar, radial	-	Independent
14	B	H	32	-	-	-	-	Right brachial plexus	-	Independent
15	B	H	48	-	-	-	-	Bilaterally peroneal	NSAID, TDL	AFO and walker
16	B	A	9	Right cruris	-	-	-	-	PS	Independent
17	G	A	55	Bilaterally cruris	-	-	-	Bilaterally peroneal	PS, NSAID	Walker
18	G	A	4	Right tight and cruris	-	Right ileum	-	Right sciatic	-	Afo
19	G	A	?	Right forearm and cruris	-	-	-	Right sciatic	GBP	AFO and walker
20	B	K	4	Left arm and forearm	-	-	-	Left brachial plexus	PS	Independent
21	G	H	34	-	-	-	-	Right sciatic	-	Afo
22	B	K	72	Right tight and cruris	-	-	-	Right sciatic	PS	Afo
23	B	H	?	Bilaterally tight	-	-	-	Right sciatic	NSAID, TDL	AFO, immobilizer and walker
24	B	K	22	Right arm and forearm	-	-	-	Right median, ulnar, radial, musculocutaneus	PS	Independent
25	G	K	17	-	-	-	-	Right fascial	-	Independent
26	B	A	9	-	-	-	-	Left sciatic and femoral	NSAID, TDL	AFO, immobilizer and walker
27	G	A	3	-	-	-	-	Bilaterally peroneal	GBP	Bilaterally foot dorsiflexion bandage
28	G	G	1	Left cruris	-	Right tibia	-		PS, NSAID, TDL	Walker
29	G	G	3	-	-	Bilaterally femur	-	-	PS, TDL	Walker
30	G	H	96	Left cruris	Left Chopart and right 5th MTF	-	-	-	PS, TDL	Prosthesis and walker

G: Girl, B: Boy, A: Adıyaman, H: Hatay, G: Gaziantep, K: Kahramanmaraş, MTF: Metatarsophalangeal, SDH: Subdural hematoma, NSAID: Non-steroidal anti-inflammatory drug, TDL: Tramadol, PS: Paracetamol, GBP: Gabapentin, AFO: Ankle-foot orthosis, KAFO: Knee-ankle foot orthosis, *Length of stay in the rubble, ?: Unknown

Table II. Characteristics of pediatric earthquake victims-2

No	Age	Gender	City	Hour*	Fasciotomy	Amputation	Fracture	Brain injury	Peripherial nerve injury	Drugs for pain control	Final ambulatuar status
31	10	G	H	1	-	-	Left femur, left 4th distal phalanx on hand	-	-	PS, NSAID	Independent
32	11	B	G	?	-	-	-	EDH	-	PS	A canadian
33	11	G	K	72	Right foot	Left transfemoral	-	-	-	TDL	Sitting independently
34	11	G	H	?	Left tight and foot	-	-	-	-	-	Independent
35	12	G	K	1	Left foot	-	-	-	-	PS, NSAID, TDL	Independent
36	12	G	H	15	Bilaterally cruris	-	-	-	Right sciatic	PS	AFO
37	12	B	A	10	-	-	-	-	Right peroneal	GBP, TDL	AFO
38	12	B	H	60	Right forearm	-	-	-	Right median, ulnar, radial, sciatic	TDL	AFO
39	13	G	K	48	-	Left transfemoral	-	-	Left radial, femoral, ulnar	-	Prosthesis and walker
40	13	G	K	?	Bilaterally cruris	-	-	-	Bilaterally sciatic	-	Bilaterally AFO
41	13	B	H	40	Right forearm	-	-	-	Right radial, median, ulnar	PS	Independent
42	13	B	A	?	Left tight and cruris	-	Left femur and 4th thoracal vertebra	-	Left femoral and sciatic	-	AFO
43	13	B	K	?	Bilaterally tight	-	-	-	Right femoral and sciatic	-	AFO and walker
44	14	G	A	1	-	-	Left ileum	-	Left sciatic, superior gluteal nerve	PS	AFO
45	14	B	A	8	Left forearm	-	-	-	Left median, ulnar, radial	PS, TDL	Independent
46	13	G	H	8	Left tight and foot	-	-	-	Left sciatic	PS, TDL	
47	14	G	A	13	-	-	-	EDH	-	PS	Independent
48	15	G	A	1	Right forearm	-	-	-	Right brachial plexus	NSAID	Independent
49	15	B	H	5	-	-	-	-	Right radial, ulnar	-	Independent
50	15	G	H	1	-	-	?Radius lomber thoracal?	-	Cauda equina syndrome	-	Bilaterally AFO
51	16	B	K	48	-	-	Left radius and ulna	-	Left axillar, suprascapular nerve	PS, TDL	Independent
52	14	B	K	42	Right tight	-	-	-	Right sciatic	PS, TDL	

Table II. Continued

No	Age	Gender	City	Hour*	Fasciotomy	Amputation	Fracture	Brain injury	Peripherial nerve injury	Drugs for pain control	Final ambulatuar status
53	16	G	A	?	Left cruris	-	Left tibia,1st,2nd,3th lomber vertebra	-	Left bracial plexus	PS	Independent
54	16	B	A	6	Right tight and cruris	-	-	-	-	TDL	Independent
55	16	G	G	3	Left forearm	-	-	-	Left brachial plexus, right femoral and sciatic, left sciatic	PS	Two canadian
56	17	B	K	1	-	-	Right 1st metatars	-	-	PS, TDL	2 canadian
57	17	B	A	40	-	-	-	-	Left brachial plexus, bilaterally sciatic	PS, TDL	Independent
58	17	G	H	42	-	-	-	-	Right sciatic	GBP, TDL	AFO and a canadian
59	17	G	H	30	-	-	-	SDH	Median, ulnar, sciatic, femoral	PS	Independent
60	17	B	H	?		-	-	-	-	PS, PGB, TDL	Prosthesis

G: Girl, B: Boy, A: Adıyaman, H: Hatay, G: Gaziantep, K: Kahramanmaraş, MTF: Metatarsophalangeal, SDH: Subdural hematoma, EDH: Epidural hematoma, NSAID: Non-steroidal anti-inflammatory drug, TDL: Tramadol, PS: Paracetamol, GBP: Gabapentin, PGB: Pregabalin, AFO: Ankle-foot orthosis, *length of stay in the rubble, ?: Unknown

Of the 60 inpatients rehabilitated in our clinic, 31 (51.7%) were girls and 29 (48.3%) were boys. The mean age of the patients was 10 (±0.76) years. Twenty-two (36.7%) of the patients experienced earthquakes in Hatay, 21 (35%) in Adıyaman, 13 (21.6%) in Kahramanmaraş and 4 (6.7%) in Gaziantep. The length of stay under the rubble of 50 patients was recorded, with a median of 12 (1-96) hours.

Crush syndrome developed in 25 (41.6%) of the patients, and 14 (23.3%) of them needed dialysis. HBOT was applied to 10 (16.6%) children. Low molecular weight heparin was used in a few of the patients, particularly those undergoing orthopedic surgery. None of the patients developed thrombotic complications due to immobilization.

Peripheral nerve damage was detected in 42 (70%) children by electro-neurophysiological or physical examination methods. Despite the difficulty of electro-neurophysiological examinations in pediatric patients, it could be applied to 34 (80.9%) of these patients. The most damaged nerve in the lower extremity was the sciatic (16%), followed by the peroneal (10.9%) and femoral nerves (3.6%). Combined damage of median, ulnar and radial nerves (12.7%) and brachial plexus damage (10.9%) were the most common nerve pathologies in the upper extremity. In addition to these; facial, axillary, suprascapular, musculocutaneous and superior gluteal nerve pathologies were also present. Twelve patients underwent control ENMG and 9 (75%) showed signs of reinnervation.

Thirty-four (56.6%) patients underwent fasciotomy. The fasciotomy sites were one lower extremity in 17 (28.3%) children, one upper extremity in 9 (15%) children, bilateral lower extremities in 6 (10.0%) children, and one upper and ipsilateral lower extremity in 2 (3.2%) children.

There were fractures in a total of 13 (21.6%) children: one lower extremity in 6 (10.0%) patients, one upper extremity in 2 (3.2%) patients, two lower extremities in 1 (1.6%) patient, one lower and one upper extremity in 1 (1.6%) patient, one lower extremity and spine in 2 (3.2%) patients, and one upper extremity and spine in 1 (1.6%) patient. One (1.6%) patient developed atlantoaxial joint subluxation, and 1 (1.6%) patient developed right 1st metatarsophalangeal (MTF) joint subluxation (patient #7 and #54 respectively).

Seven (11.6%) patients had amputations in various parts of the extremities. The amputation level was transfemoral in 2 (3.2%) patients, transhumeral in 1 (1.6%), hip disarticulation in 1 (1.6%), transtibial in 1 (1.6%), Chopart and other 5th MTF joint in 1 (1.6%) patient and 1 (1.6%) had transmetatarsal (TMT) amputation. None of the amputees developed any complications which may occur after amputation (phantom pain, phantom sensation, contracture, edema, etc.).

Five (8.3%) of the patients had varying degrees of traumatic brain injury. Spinal cord damage was not detected in any of our patients.

Discussion

On February 6th, 2023, two major earthquakes occurred on the same day in Kahramanmaraş in southeastern Turkey. In this major disaster which resulted in thousands of dead and injured, the treatment of musculoskeletal traumas included medical treatment, debridement, fasciotomy, open or closed reduction and amputation, and the importance of post-disaster rehabilitation services once again emerged.

The first of the patients we examined in our study was admitted on the 5th day after the earthquake. In our 25-bed Pediatric Rehabilitation Clinic, a total of 60 patients were hospitalized and treated within the specified period.

After detailed evaluation, pain control was provided to all patients and necessary exercises were performed to prevent the possible effects of immobilization. For pain control, paracetamol, topical or oral non-steroidal anti-inflammatory drugs, tramadol, gabapentin and pregabalin were preferred as single or in combination medication. Exercises to maintain range of motion and muscle strength, appropriate physical therapy agents for fracture healing, therapeutic electrical stimulation in cases of nerve damage, balance and ambulation training, hydrotherapy, and appropriate bandaging for stump formation in amputees were applied. During the hospitalization of three patients in our clinic, prostheses were provided and prosthesis training was given.

In a study examining 33 pediatric patients who were transferred to a Pediatric Surgery Clinic after the 1999 Marmara earthquake, it was reported that 16 of the children were female and 17 were male, with a mean age of 8.8±0.75 years (6). In that study, the mean duration of stay under the debris was 30 hours (1-110 hours). While the cases in that study were similar to our patients in terms of gender, it was observed that their mean age was lower and the duration of stay under the rubble was longer than in our cases. In that same study, only 6 patients underwent fasciotomy, and it was stated that no amputation was performed on any of the children. Peripheral nerve damage was reported in 3 children, fractures in 8 children, and central nervous system damage in 8 children (6). Except for central nervous system damage, all injuries were more common in our cases. The study we mentioned included patients in a Pediatric Surgery Clinic, not a Rehabilitation Clinic, and the number of patients was fewer. These may be the reasons for the differences between the two studies.

In a study presenting musculoskeletal injuries after the 2008 Wenchuan earthquake, 205 cases were examined and peripheral nerve damage was reported in 20 percent of the cases (7). In a study by Uzun et al. (8), in which electrophysiological examinations of 12 pediatric cases affected by the 1999 Marmara earthquake were evaluated, brachial plexus damage was reported in 2 patients and peripheral nerve damage in 10 patients. In these two studies, similar to our study, the sciatic and peroneal nerves were the most affected peripheral nerves. In the aforementioned study of Uzun et al. (8), check-up ENMG was performed on 8 patients and regeneration findings were observed in 5 of them. We were able to perform check-up ENMG on 12 of 34 patients on whom we performed baseline ENMG evaluation and found reinnervation findings in 9 of them. The fact that the Kahramanmaraş-centered earthquake affected a wider region and our hospital is located in a province far from the earthquake zones, the difficulties experienced by the discharged patients in coming to our hospital for check-up examinations may have led to the low number of patients who underwent check-up ENMG.

In the study of Uzun et al. (8), the problems seen in adult and child patients after this disaster were also compared, and it was revealed that children in this age group stayed under the rubble longer and compartment syndrome was more common. Additionally, in the same study, it was reported that since the adult group has more muscle mass, muscle breakdown and therefore crush syndrome were more common in adults than in children (8). Although there are a few studies in the literature examining affected children or adults after a disaster such as an earthquake; to our knowledge, there is no study directly examining the experience of a pediatric rehabilitation clinic (1-6). Such differences have led to the need to examine the pediatric age group in more detail. Our work is important in this respect. Some of the patients we followed have given us new experiences as clinicians. We aim to share a few of them below:

First of all, the most common musculoskeletal pathology in our patients was peripheral nerve injuries. ENMG is an important test which can guide diagnosis, treatment planning, prognosis and follow-up. This requires clinical experience, and it can only be applied to more selective cases compared to adults due to the limited tolerance of the pediatric patient group to this painful examination, and the difficulty of working in smaller areas (9-11). The patients we evaluated with ENMG had different levels of single or combined peripheral nerve damage. While most of these patients had axonal damage and progressed very slowly, a few of the children had only neuropraxia without axonal damage. Due to the difficulties in ENMG examination in the pediatric population previously mentioned, we did not perform a check-up ENMG on patients with neuropraxia, and they recovered rapidly within one to two months.

We struggled with NP in many cases due to damage to peripheral nerves. The most challenging case for us in terms of NP was case 57. The patient with left brachial plexus and bilateral sciatic nerve injury had NP which disrupted sleep and activities of daily living (ADL). The NP of the patient, whose LANSS Scale was 19/24 before rehabilitation, was so severe that it was observed that he had self-mutilation. The patient's physical therapy program included: joint range of motion to the left upper and bilateral lower extremities, stretching, strengthening exercises, electrical stimulation, occupational therapy, electrotherapy to the left lower extremity and desensitization to the left sole of the foot. At admission to our clinic, the patient was using tramadol 2x100 mg/day iv and paracetamol 10 mg/mL 2x1/day iv. Gabapentin was started due to severe NP and the dose was gradually increased to 1.800 mg/day. The patient, who could not sleep for more than 15 min-1 hour for days, was first started on zopiclone 7.5 mg/day with the recommendation of psychiatry, was changed to quetiapine due to unresponsiveness and the dose was increased to 50 mg/day. Radiofrequency ablation was performed first on the left posterior tibial nerve and then on the left sciatic nerve on the patient but the complaints continued. When NP continued despite all these treatments, 4x10 cc bupivacaine was administered first with a popliteal catheter and then with an epidural catheter. As the patient's complaints continued, bupivacaine was stopped and oxycodone 3x5 mg was started. The medical treatment of the patient, who had difficulty in ADL due to NP and had sleep problems, was through psychiatry and algology consultations with tramadol 2x100 mg/day iv, gabapentin 1.800 mg/day po, quetiapine 25 mg/day po, oxycodone 3x5 mg/day po, duloxetine 30 mg/day po, lorazepam 1mg/day po, pantoprazole 40 mg/day po and 250 mg B1/250 mg B6/1 mg B12 po. After two months of pharmacological, non-pharmacological and algological treatments, an increase in ADL and sleep duration and a decrease in NP level were observed. After the treatment, the patient with a LANSS Scale of 8/24 was discharged while walking independently.

In addition, patients 11, 24, 41 and 46 were consulted to the Hand Surgery Clinic due to multiple nerve damage and tissue defect in the forearm. Patient 46 had a functional muscle transfer from the latissimus dorsi muscle to the forearm. Their splints were revised and they were continuing to receive physical therapy at the time of writing.

Another common type of musculoskeletal injury associated with earthquakes is fractures. In our patients, the fracture site was mostly in the lower extremity, similar to the literature (12). Patient 29 was operated under emergency conditions because of right femoral shaft and left intertrochanteric femur fractures. The patient, who was recommended to be immobilized for 4 weeks postoperatively, was recommended to be immobilized for 4 more weeks after orthopedic consultation, and then the patient was re-operated because there was insufficient callus formation on the left side on X-ray. After that, immobilization was recommended for another 6 weeks. In the follow-up X-ray, sufficient callus formation did not form and she was operated on for the third time and remained immobile for about 6 weeks. During the immobilization period, knee and ankle joint range of motion exercises, ankle pumping exercises and frequent position changes were applied in order to prevent decubitus formation. The patient started walking with partial weight bearing with a walker with control graphs and orthopedic consultations. The patient was still being rehabilitated in our clinic at the time of writing.

In post-earthquake musculoskeletal disorders, after soft tissue disorders, peripheral nerve injuries and fractures, there were amputations in our patient group, similar to the literature (4,7,13). Preparation of the stump for prosthesis, prescription of the appropriate prosthesis and adaptation to a prosthesis were included in our rehabilitation plan.

Kinesiophobia was another of the issues we tried to deal with during the walking training of these children who had experienced major traumas materially and spiritually and remained immobile for a long time. Kinesiophobia was prominent especially in patients 17, 35 and 36. Reflex Sympathetic Dystrophy syndrome Type-1 developed in the left foot of patient 35, and electrotherapy was added to the

treatment in addition to weight-bearing exercises. Their fear of movement and pain decreased and their mobilization skills improved over time.

Most of the children were in serious need of psychological support due to the loss of family members or the disruption of their own physical integrity and were provided with both medical treatment and psychological support through relevant consultations.

In addition to all these, the renal function values and electrolytes of the patients who needed hemodialysis before admission to our clinic were at normal levels during their hospitalization.

Conclusion

We believe that performing rehabilitation treatments after natural disasters such as earthquakes and planning these practices specifically for earthquakes are important. In the pediatric population, which is a rare patient group due to its features in both follow-up and treatment, musculoskeletal injuries caused by earthquakes and their complications are very important in the development and realization of disaster rehabilitation strategies. However, multicenter studies including long-term follow-up results of these patients are needed.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Ankara Etlik City Hospital (date: 20.06.2023, approval number: AEŞH-EK1-2023-265) before the study, and the study was conducted in accordance with the rules of the Declaration of Helsinki.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Z.K.Ü., K.K., E.A., E.Ü.A., Concept: Z.K.Ü., K.K., E.A., E.Ü.A., Design: Z.K.Ü., E.A., E.Ü.A., Data Collections or Processing: Z.K.Ü., K.K., E.A., E.Ü.A., Analysis or Interpretation: Z.K.Ü., E.A., E.Ü.A., Literature Search: Z.K.Ü., E.Ü.A., Writing: Z.K.Ü., E.Ü.A.

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Original Article

Assessment of Clinical and Laboratory Predictors for Chronic Childhood Immune Thrombocytopenia

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ABSTRACT

Aim: To determine the risk factors associated with chronic childhood immune thrombocytopenia (ITP).

Materials and Methods: We retrospectively analyzed the medical records of 123 children with ITP who were admitted to our Department of Pediatric Hematology between May, 2006 and May, 2019. We evaluated their demographic, clinical, and laboratory characteristics, and assessed the risk factors associated with chronic ITP in childhood.

Results: Of the 123 children with ITP, 60.2% were male, with an average age of 6.4±4.0 years. At follow-up, 93 (75.6%) of the patients were diagnosed as acute ITP, whereas 30 (24.4%) progressed to chronic ITP with a platelet count of lower than 100×10^9/L at the end of the 12-month follow-up period. Older age at admission [Odds ratio (OR): 1.4, 95% confidence interval (CI): 1.2-1.6, p<0.001], female gender (OR: 4.1, 95% CI: 1.5-10.3, p=0.003), and insidious onset of the symptoms (OR: 5.0, 95% CI: 1.1-22.6, p=0.03) were determined to be risk factors for chronic ITP.

Conclusion: Our study indicates that older age, female gender and insidious onset of the disease at admission may predict chronic ITP in childhood.

Keywords: Immune thrombocytopenia, risk factors, children

Introduction

Childhood immune thrombocytopenia (ITP) is an immune-mediated disorder characterized by an isolated decrease in platelet levels (<100×10^9/L) in the absence of other causes of thrombocytopenia (1,2). The overall incidence of ITP in children under 18-years is reported to be 8.8 per 100,000 person-years (3). ITP is idiopathic in most cases, but some children may present following a viral infection or immunization (4,5). Clinical manifestations are related to the severity of thrombocytopenia and include purpura and also life-threatening bleeding episodes in rare cases.

Currently, the pharmacological treatment for ITP is recommended in children with significant bleeding regardless of platelet count (4,5). ITP typically has a benign course in childhood and most recover at 6-18 months after diagnosis. However, in 20-30% of patients, it progresses to chronic ITP, defined as the persistence of thrombocytopenia (<100×10^9/L) for more than 12 months (1,2).

Once diagnosed, those children with chronic ITP, and their families, often experience a range of physical and emotional difficulties while they try to cope with the fear of relapse of the disease.

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Chronic ITP may be associated with several pharmacological, laboratory, and genetic factors such as age, gender, onset type, previous vaccination or viral infection, platelet counts at admission, and treatment with IVIG and/or steroids (1,6-8). Determining the predictive factors for chronic disease may be beneficial for the patients, their parents and the treating physicians.Therefore, in this study, we aimed to identify those risk factors which predict childhood chronic ITP.

Materials and Methods

This was retrospective cohort study conducted at a single center of a tertiary hospital in Turkey, between May, 2006 and May, 2019. During the 13-year study period, a total of 123 children with newly diagnosed ITP, with a platelet count of $<100\times10^9$/L, who were followed up at the Department of Pediatric Hematology were included this study. Patients with secondary thrombocytopenia or without isolated thrombocytopenia, <12 months or >18 years of age, those with insufficient data on file, and those who did not continue their regular follow-up at the outpatient clinic of pediatric hematology were excluded from this study.

The diagnosis of primary ITP was defined through patient history, physical examination, and laboratory tests which revealed isolated thrombocytopenia without any other underlying causes (1). Disease onset was noted as abrupt (duration of clinical findings <14 days at presentation) or insidious (clinical findings for ≥14 days at admission) (1,2). Data on hemoglobin, mean platelet volume (MPV), and platelet distribution width (PDW) values obtained at the time of admission were recorded. The first-line therapy of ITP for children includes oral/IV standard-dose corticosteroids, a short course of high-dose steroids, and IVIG (5). Those patients whose platelet counts were below 20×10^9/L and/or with significant bleeding symptoms received an IVIG dose of 1 g/kg for 2 days. Oral steroid was given at a dose of 1-2 mg/kg/day for 30 days or as 4 mg/kg/day for 4 days, while high-dose IV methylprednisolone (15-30 mg/kg) was administered via 30-60 minute bolus infusion for 3 days. IVIG plus IV methylprednisolone was the definition of the combined strategy (5). A bone marrow aspiration was performed to rule out other causes of thrombocytopenia if the patients displayed unusual symptoms or had a poor response to IVIG. Additional tests such as autoimmune screenings were performed in those patients who were refractory to treatment.

After discharge, all patients were followed up at our outpatient clinics of pediatric hematology for at least for 12 months. Chronic ITP was defined as persisting thrombocytopenia of less than 100×10^9/L lasting for more than 12 months and persistent ITP referred to those patients who did not achieve spontaneous remission or did not respond fully to treatment for 3 to 12 months after diagnosis (9). Medical data on age at admission, gender, season, family history of ITP, history of antecedent infection (4 weeks before admission), or recent vaccination (3 months before diagnosis) (1,2,5) were recorded on previously prepared forms. Laboratory analyses, presenting symptoms, and therapy options (steroid, IVIG, or combination) were noted. The acute and chronic ITP groups were compared in terms of their demographic, clinical and laboratory characteristics. Then, possible risk factors for chronic ITP were determined.

This study received approval from the Ege University Medical Research Ethics Committee and was conducted in accordance with the 2013 Helsinki Declaration guidelines.

Statistical Analysis

SPSS software for Windows version 23.0 was used to analyze all the data (IBM, Armonk, NY: IBM Corp.). Descriptive statistics were used including mean (with standard deviations) and median (range: minimum-maximum) for continuous variables, and counts (percentages) for categorical variables. The conformity of the data to the normal distribution was evaluated with the Kolmogorov-Smirnov test. Initially, Student's t-test and the Mann-Whitney U test were used to compare continuous variables for parametric and non-parametric variables, respectively. The chi-square test was used for categorical variables. Receiver operating characteristic (ROC) analysis was performed for the importance of age in the differentiation of acute and chronic ITP cases. Next, the risk factors for chronic ITP were analyzed using the stepwise method in multivariate logistic regression analysis. The independent variables included in the model were those that were found to be significant (≤0.01) in univariate analyses. Results from the regression are reported as odds ratios (ORs) with 95% confidence intervals (CIs). All reported p-values are 2-sided. Statistical significance was set at p-values of less than 0.05.

Results

Of 123 patients, the female-to-male ratio was 0.66; 74 (60.2%) of the patients were male, and 49 (39.8%) were female. The mean age of the patients was 6.4±4.0 years (range; 1-15 years). According to ROC analysis, the area

under the curve was 0.840, sensitivity was 80%, specificity was 89.25% and the best cut-off point was determined to be 9 years of age. At admission, abnormal physical findings were identified in 111 (91.0%) of the patients; 12 (9%) children had a diagnosis of ITP based only on their laboratory results. Petechiae, ecchymosis, and purpura were detected in 95 patients (77.3%), while 28 (22.7%) had epistaxis and dental bleeding. At admission, presenting symptoms were present for longer than 2 weeks (insidious onset) in 22 of the patients (17.9%).Initially, the mean platelet count for all patients was 33.5±30.5×10^9/L, (range: 2-123×10^9/L), with a MPV of 8.9±1.6 fL (range: 0-20.2). Thirty-eight patients (30.9%) required bone marrow aspiration; and of these, 35 patients (92.1%) had increased megakaryocyte production. At follow-up, among the 123 patients, 93 (75.6%) were defined as acute ITP, while 30 (24.4%) progressed to chronic ITP with a platelet count of lower than 100×10^9/L at the end of the 12-month follow-up period. Although this study focused on newly diagnosed and chronic ITP patients, there were 25 cases that could be defined as persistent according to the data collected (platelet count below 100,000 at 6 months). All of these 25 patients were diagnosed as chronic ITP at the end of 1-year follow-up.

After the diagnosis of ITP, 92.7% of the patients received treatment (n=114), while 9 (7.3%) were followed up without any medication (i.e., wait-and-see approach). Among the treated patients, 85 (74.6%) were given IVIG, 22 (19.3%) had combined treatment (steroid + IVIG), and 7 (6.1%) had only steroid treatment.

Clinical course of the disease and risk factors for chronic ITP

In univariate analysis, the average age of those patients with acute ITP was lower than that of those with chronic ITP (5.0±2.9 vs. 10.7±3.7 years, p<0.001). Female patients had a higher prevalence of chronic ITP (40.8% vs. 13.5%, p=0.001). The rate of abrupt onset of symptoms was substantially higher in those individuals with acute ITP (95.2% vs. 18.6%, p=0.018). There were clinical signs in 11 (36.6%) of the 30 cases who developed chronic ITP.At admission, hemoglobin levels, platelet count, MPV, and PDW were similar in those patients with acute and chronic ITP. However, WBC count was higher in those patients with acute ITP (9.0±3.2 10^3/μL vs 7.7±2.7 10^3/μL) (p=0.027). Thirty patients (24.4%) underwent antinuclear antibody (ANA) testing, with a 43.3% (n=13) positivity rate. There was no significant difference in terms of ANA positivity between acute and chronic ITP (p=0.17). There was no significant difference regarding the type of treatment given at the time of diagnosis (p=0.111) (Table I). Four patients with chronic ITP required splenectomy. Splenectomy enabled full recovery in only one case; the others were still on combined treatment.

Chronic ITP risk factors were investigated by using logistic regression analysis. In the multivariate model, it was found that the risk of chronic ITP was greater with increasing age (OR: 1.4, 95% CI: 1.2-1.6, p<0.001). In the age-adjusted model, girls were at 4.1 times higher risk of chronic ITP (95% CI: 1.5-10.3, p=0.003) and insidious onset at admission was associated with the chronicity of the disease (OR: 5.0, 95% CI: 1.1-22.6, p=0.03) (Table II).

Table I. Comparison of the clinical and laboratory characteristics of patients with acute and chronic ITP

Variables	Acute ITP (n=93)	Chronic ITP (n=30)	p-value
Age at diagnosis (year)†	5.0±2.9	10.7±3.7	<0.001
Gender Female Male	 29 (59.2) 64 (86.5)	 20 (40.8) 10 (13.5)	 0.001
Family history of ITP‡	6 (6.4)	4 (13.3)	0.250
Antecedent infection‡	73 (78.4)	26 (86.6)	0.320
Recent vaccination‡	8 (8.6)	1 (3.3)	0.450
Abrupt onset‡	79 (95.2)	7 (18.6)	0.010
Season (Winter + spring)‡	60 (64.5)	24 (80.0)	0.110
Any clinical finding‡	83 (89.2)	29 (96.7)	0.290
Laboratory values			
Platelets ×10^9/L†	34.5±3.2	30.3±2.1	0.420
Hemoglobin (g/dL)†	10.8±1.3	11.3±1.3	0.080
WBC ×10^3/μL†	9.0±3.2	7.7±2.7	0.020
MPV (fl)†	8.8±1.8	9.0±1.2	0.430
PDW†	15.6±2.5	16.0±0.9	0.200
Type of treatment‡			
IVIG alone	66 (78.6)	19 (63.3)	0.210
Steroid	5 (6.0)	2 (6.7)	
IVIG plus steroid	13 (15.4)	9 (30.0)	

‡: n (%), †: mean ± standard deviation
ITP: Immune thrombocytopenia, IVIG: Intravenous immunoglobulin G, MPV: Mean platelet value, PDW: Platelet distribution width, SD: Standard deviation, WBC: White blood cell

Table II. Logistic regression analysis results of the risk factors for chronic ITP among all study patients

	OR	95% CI	p-value
Age	1.4	1.2-1.6	<0.001
Gender Female (ref) vs. Male	4.1	1.5-10.3	0.003
Clinical findings Abrupt (<2 weeks) (ref) vs. Insidious (>2 weeks)	5.0	1.1-22.6	0.035
WBC count (at admission) <6.0x10^3/µL (ref) vs. ≥6.0x10^3/µL	2.5	0.7-8.5	0.120

CI: Confidence interval, ITP: Immune thrombocytopenia, WBC: White blood cell, OR: Odds ratio

Discussion

In this retrospective cohort study, we evaluated the predictive risk factors for chronic ITP among 123 children who were followed up at the Department of Pediatric Hematology of our hospital. Although the majority of children with ITP showed a full recovery, about 20-25% of the cases experienced persistent thrombocytopenia lasting longer than a year following diagnosis (8-10). Shaw et al. (3) investigated the incidence and clinical burden of ITP in children in the United States and reported that nearly one-third (32.4%) of cases with ITP appeared to be persistent (lasting 3-12 months); and 15.9% had evidence of chronic ITP (lasting >12 months) during follow-up. In another study, Alam (8) evaluated the records of 95 children between 0-15 years over a 10-year period and reported that only 5 (5.3%) developed chronic ITP. In the current study, 30 out of 123 patients (24.4%) had a diagnosis of chronic ITP. Due to the high impact of ITP on a child's everyday life, as well as being able to decide which treatment should be initiated, there is a critical need to predict the course of childhood ITP in order to guide the patients, the parents, and the treating physicians. Heitink-Pollé et al. (10) conducted a meta-analysis, reviewing and evaluating all clinical, laboratory, pharmacologic, and genetic determinants over the course of childhood ITP. They reported the predictive factors as being at an older age at the time of diagnosis, female gender, no history of infection or vaccination, insidious onset, higher platelet counts at presentation (>20×10^9/L), and positive ANA titers.

In a review on ITP, it was suggested that infants had a better chance of having a short duration of the disease, while adolescents had a higher risk of chronic disease (7). In the current study, similarly, we found that that the risk of chronic ITP was greater with increasing age (OR: 1.4, 95% CI: 1.2-1.6).

ElAlfy et al. (11) found that females more than 10 years of age were more susceptible than males in terms of following a chronic course. However, Yaprak et al. (12) studied a total of 350 children (186 females, 164 males) between the ages of 6 months and 16 years and did not find a gender predominance related to chronic ITP. In our study, the female gender was found to be a predictive factor for the development of chronic disease.

Some studies demonstrated significant associations with the absence of antecedent infection and the insidious onset of symptoms with the development of chronic ITP. Revel-Vilk et al. (13) found that a short course of ITP was associated with the presence of clinical symptoms 2 weeks prior to the disease and a younger age. Similar studies also demonstrated that the age at diagnosis, the duration of the clinical findings at diagnosis, and short-term recovery from ITP were powerful predictors (14-17). In our study, a longer duration of symptoms at diagnosis was a predictive factor for the development of chronic disease. We also evaluated the season in which patients showed their first symptoms, but no significant relation with chronic ITP was found, as was also stated in a meta-analysis (10).

In ITP, megakaryocytes produce platelets in response to an increased demand and newly generated platelets have a bigger size. Hence, platelet indices including MPV, PDW may provide vital information for megakaryopoietic activity in ITP (18,19). Tang et al. (18) showed that when the optimal cut-off points of MPV were equal to or larger than 9.35 fL, diagnosis of ITP had a sensitivity of 70.3% and a specificity of 74.8%. Chen et al. (20) found a non-linear connection between MPV and ITP relapse, with the inflection point being 21 fL. However, Söğüt et al. (16) reported that they observed no significant relationship between hematological parameters such as platelet, WBC, and MPV and the chronic course of ITP. In our study, similar to Söğüt et al.'s (16) study, there was no difference between patients with acute and chronic ITP in terms of the MPV value detected at admission (acute ITP: 8.8±1.8 fL, chronic ITP: 9.0±1.2 fL, p=0.43). WBC counts in both groups were within normal ranges (acute ITP: 9.0±3.2×10^3/µL, chronic ITP: 7.7±3.2×10^3/µL, 0.02), despite being greater in those patients with acute ITP. In further analysis, WBC count was not found to be a risk factor for chronic ITP.

In our country's and many international guidelines, steroids are recommended as the first-line treatment for patients with ITP who require pharmacological treatment. However, the 2019 American Society of Hematology guideline for children with ITP includes IVIG as a first-line

treatment in addition to steroids. The guideline states: "For children newly diagnosed with ITP with non-life-threatening mucosal bleeding and/or decreased health-related quality of life, the ASH Guideline Panel recommends anti-D immunoglobulin or IVIG". Treatment recommendations for ITP can be flexible according to guidelines and patient needs. Although steroid therapy predominates in clinical practice, IVIG can reduce the risk of progression to chronic ITP and favorably affect prognosis. It has been hypothesized that IVIG prevents the onset of chronic illness because of its long-lasting immunomodulatory effects, which include an increase in the quantity and functionality of regulatory T cells (21,22). Yacobovich et al. (7) also stated that IVIG therapy may alter the disease's clinical course by restoring the immunologic balance and activating regulatory T cells. In addition, IVIG acts relatively quickly, usually within a few days, to increase platelet counts in ITP patients. This can be particularly useful when the patient needs a rapid increase in platelet counts, such as during bleeding episodes or before surgery. Finally, steroids such as prednisone have several side effects when used long-term or at high doses, including weight gain, psychiatric symptoms, hyperglycemia, osteoporosis, and immunosuppression. In contrast, IVIG is generally well tolerated and has fewer systemic side effects (9). The more widespread use of IVIG treatment in our study may be due to these reasons.

In our research, 75.6% of the patients were defined as acute ITP, while the remaining 24.4% developed chronic ITP. Since the majority of our patients required treatment, we chose IVIG as the first line of treatment. We did not find any significant difference between the treatment type and progression to chronic ITP.

Secondary treatment options are used in those patients who do not respond to primary treatment. Rituximab may be used if there is no response to primary treatment (IVIG, anti-D, conventional dose steroid) and bleeding persists (level of evidence 2C). As in patients with chronic ITP, rituximab is recommended as an option for splenectomy or in patients who do not respond to splenectomy (level of evidence 2C). However, second step therapies such as rituximab and splenectomy are not without significant adverse effects (4). Splenectomy is performed if there is life-threatening bleeding which is unresponsive to treatment in acute ITP, or if there is a platelet count of $<30\times10^9$/L in chronic ITP at 12 months of follow-up. Splenectomy rates have been steadily decreasing over time with the increased use of pharmacologic therapies (23). As splenectomy may offer a high efficacy with a partial response rate of 83% and a complete response rate of 74%, the outcome and the associated risks cannot be predicted in a given patient (24). Consistent with this trend, only four patients in this cohort underwent splenectomy.

Traditional ITP treatment strategies have been based on reducing increased platelet destruction. However, in recent years, after cell culture studies showed that, contrary to expectations, increasing TPO levels in ITP patients was not sufficient, methods based on increasing platelet production have been added to the secondary treatment policy. Romiplostim and Eltrombopag increase platelet production by activating TPO. Romiplostim is used in doses of 1-10 µg/kg once a week as a subcutaneous injection. The response occurs in 1-4 weeks and is maintained as long as the drug is continued. Eltrombopag is used orally at 25, 50, and 75 mg/day doses. Its effect starts after the second week. Both drugs have similar effects in patients with or without splenectomy. Easily manageable side effects such as headache, fatigue, epistaxis, nosebleeds, and arthralgia may occur in 20% of patients on these drugs. However, the main adverse effects of TPO agonists are a 10% decrease in thrombocytopenia from baseline after discontinuation of the drug ("rebound" thrombocytopenia), an increase in reticulin fibers in the bone marrow, and thrombotic complications. Hepatic impairment may be observed in 13% of patients using Eltrombopag. Safety data on the long-term use of these drugs are not yet sufficient (25). Additionally, data on their use in children are very limited (26).

Study Limitations

Our study has some limitations. First of all, a relatively small number of patients at a single center from Turkey constitute the research population; therefore, care should be taken while generalizing these results. Secondly, our study is based on a review of medical records due its retrospective nature. Existing data regarding the pre-admission infection history, severity and duration of bleeding at admission, and the type of treatment were extracted from the patients' files. Of course, how they were recorded by the clinician affects the reliability of this data. Finally, the lack of data on the use of second-line therapies in the patients included in this study limits the ability to comment on the prognosis in ITP patients. The data used in our study were collected retrospectively. The treatment modalities used in ITP patients may vary according to the clinical conditions of the patients, the side effects of the drugs, the patients' and relatives' preferences, and the physicians' experiences and preferences. The reasons why second-line treatments were not preferred in our study may be the relatively mild clinical

course of the patients included in this study, concerns about the side effects and risks of secondary treatments, insufficient follow-up periods, the previous treatment experiences of the physicians, and complex insurance and reimbursement procedures.

Conclusion

In conclusion, older age at diagnosis, female gender, and insidious onset of symptoms were significantly associated with the development of chronic ITP in our patients. We determined that these three factors might guide pediatricians in clinical practice as predictive factors for the chronicity of ITP.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Ege University Faculty of Medicine Clinical Research Ethics Committee (approval no: 19-4.1T/17, date: 17.04.2019).

Informed Consent: The written informed consent could not be taken from the patients due to the retrospective design of the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: S.A., H.G., Design: S.A., H.G., Data Collection or Processing: S.A., H.G., Analysis or Interpretation: S.A., H.G., Literature Search: S.A., H.G., Writing: S.A., H.G.

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Original Article

Clinical and Parental Characteristics of Hospitalization in Children and Adolescents with Autism Spectrum Disorder

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ABSTRACT

Aim: The aim of this study was to compare inpatient and outpatient cases diagnosed with autism spectrum disorder (ASD) and to show which factors were more associated with hospitalization in children and adolescents.

Materials and Methods: We included 85 outpatient and 34 inpatient children and adolescents with ASD. Psychiatric diagnoses were assessed with the K-SADS-PL. Factors relevant to the hospitalization of ASD cases were evaluated with a logistic regression model.

Results: The Childhood Autism Rating Scale scores (p=0.002), comorbid psychopathology (p=0.04), multiple psychotropic medication (p=0.001), and psychopathology of the parents (p<0.001) and siblings (p=0.029) were higher, and the education levels of the mothers (p=0.017) were lower in the inpatient-ASD group. The logistic regression model showed that the psychopathology of the mother (odds ratio=10.293, p<0.001) was associated with psychiatric hospitalization.

Conclusion: It is very important to provide psychiatric and psychosocial support especially to mothers during the inpatient treatment process in addition to outpatient family support.

Keywords: Child and adolescent mental health, neurodevelopmental disorder, autism spectrum disorder, hospitalization, mental health service

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by significant difficulties with the social communication and interaction domain, and restricted, repetitive patterns of behaviors, interests and activities (1). It is about 4 times more prevalent among boys than among girls and it is observed in approximately 1 out of 27 boys and 1 out of 114 girls (2). Similar to the increasing prevalence rates, an increase has been reported in psychiatric and non-psychiatric emergency department (ED) visits in children and adolescents with ASD (3,4). Liu et al. (4,5) reported that for adolescents with ASD between the ages of 12 and 21, there were over four times more ED applications than for those without ASD, and prescriptions for two or more classes of psychotropics medication also predicted higher numbers of ED visits. In line with the higher number of ED visits, the rate of hospitalization also increased significantly and this was largely due to psychiatric conditions (6).

Besides the core symptoms of ASD, additional psychiatric diagnoses are also found in the majority of individuals. Leyfer et al. (7) stated that at least one

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psychiatric diagnosis was reported in 72% of cases aged between 5 and 17 years with a diagnosis of ASD, and also Simonoff et al. (8) found 70% of children with ASD had a minimum of one comorbid condition. Attention-deficit/hyperactivity disorder (ADHD), anxiety disorders, depression, sleep-wake disorders, obsessive-compulsive disorder (OCD), conduct disorders and bipolar disorder were reported as being common comorbid diagnoses among the ASD population (9-11). While the prevalence of intellectual disability (ID) in children and adolescents with ASD varies according to studies, Maenner et al. (2) reported 33% of cases had ID. In terms of psychotropic medication, children with ASD were nearly 9 times more likely to use psychotherapeutic medications than children without ASD (12).

Approximately 25% of those children and adolescents diagnosed with ASD have a history of psychiatric hospitalization and 11% of the patients diagnosed with ASD have a history of hospitalization in the psychiatry service between the ages of 0-21 years (13,14). Croen et al. (12) reported that children with ASD had 12 times more psychiatric inpatient hospital days than children without ASD. Examining the factors related to hospitalization in children and adolescents with ASD can determine potential intervention points which can reduce the need for the hospitalization of children with ASD (15).

In some studies, the risk of hospitalization was found to be higher in patients with ASD who had aggressive and self-destructive behaviors, late diagnoses, were adopted, or those who had a psychiatric comorbidity such as ADHD, ID, or OCD (15-17). Croen et al. (12) reported that the most common discharge diagnoses for psychiatric hospitalizations were mood disorders, psychotic disorders, and impulse disorders for children with ASD. In a study by Righi et al. (18) comparing outpatients and inpatients with ASD in terms of individual and family characteristics, it was shown that the presence of ID and mood disorders was more common in inpatients.

Knowing the characteristics and risk factors of those patients in need of inpatient treatment is important in order to reduce the need for hospitalization. Also, it may contribute to the development and improvement of the services designed for those patients who need hospitalization. In this study, we aimed firstly to compare outpatient and inpatient children and adolescents diagnosed with ASD in terms of their individual, clinical, and parental characteristics and secondly to investigate those factors associated with hospitalization in Turkey, the bridge between eastern and western cultures. We tested these hypotheses: Are the symptom severity, intellectual functioning, the presence of medical illness, comorbid psychiatric disorders, psychopathology history in the parents of the patients with ASD and polypharmacy in the inpatient ASD group higher than in the outpatient ASD (OP-ASD) group?

Materials and Methods

Participants

All participants were recruited from Ege University Faculty of Medicine Hospital. Children and adolescents with ASD, aged between 4-18 years, who were treated in the Inpatient Service (n=34) and those who were being followed up at the Ege University Faculty of Medicine Hospital (n=85) were included in this study. The files of 338 cases, which included the diagnosis and treatment processes of the patients between 2013-2019, were evaluated for the inpatient ASD (IP-ASD) group by the authors. According to the file records, 34 patients diagnosed with ASD according to the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5), and who did not have any other genetic syndromes or chromosome anomalies were selected for inclusion. The parents and participants were verbally informed about the aims of this study, and written informed consent was obtained from the parents in accordance with the Declaration of Helsinki.

For the OP-ASD group, the files of children and adolescents who were followed up with a diagnosis of ASD in the neurodevelopmental disorders outpatient clinic between 2013-2019 were evaluated randomly and they were invited onto this study during their routine polyclinic examinations or by telephone. Of the 124 ASD cases invited, the parents of 85 subjects agreed to participate and were included in this study.

Instruments

Childhood Autism Rating Scale (CARS)

The scale consists of 14 functional areas and a final general category referring to 'degree of autism'. Each item is graded with a half-degree scoring between 1 and 4, based upon the abnormality degree of observed behavior. Scoring of the scale is between 15 and 60. Scores of 30-36 indicate mild to moderate autism and scores above 36 indicate severe autism (19,20).

Schedule for Affective Disorders and Schizophrenia for School Aged Children, Present and Lifetime Version (K-SADS-PL)

K-SADS-PL is a semi-structured interview form to diagnose psychopathologies in children and adolescents according to DSM-5-TR criteria (21,22).

Wechsler Intelligence Scale for Children-Revised Form (WISC-R)

WISC-R, developed by Wechsler (23) in 1949, was revised in 1974 and became applicable to children between 6 and 16 years of age. Standardization and norms were adapted for the Turkish sample (24).

Ankara Developmental Screening Inventory (ADSI)

ADSI was developed to assess the developmental levels of Turkish children (25). It is administered to the caregiver and consists of 154 items for the assessment and evaluation of language, cognitive, fine and gross motor, communicative, social and self-care skills in children aged between 0 and 6 years.

Case Report Form

This form was composed by the authors in order to record the demographic, clinical and parental characteristics of the participants.

Assessment

The diagnostic ASD evaluation and interview of the cases were completed according to a form that was developed based on DSM-5 criteria (1). The OP-ASD group, firstly, were evaluated during their routine clinic examination, including an observation of the children via DSM-5 and an observation of the children in a playroom. Secondly, the diagnoses of the cases were re-evaluated by two of the authors with 20 years of experience in the diagnosis and follow-up of ASD, and the diagnoses were confirmed.

The IP-ASD group were diagnosed according to DSM-5 diagnostic criteria. The parents of 34 patients who met the study criteria were contacted and their files were examined after informed consent was obtained. The sociodemographic and clinical characteristics of the patients were reviewed from the patients' files. CARS, K-SADS, WISC-R, and ADSI results, which were determined during hospitalization, were obtained from the files. Diagnosis was also confirmed by two of the authors.

The presence of psychiatric disorders and/or psychopharmacological agent use was considered as a factor for the presence of psychopathology in the family. Sports participation status such as doing gymnastic exercises, bike riding, swimming, walking, or running were investigated and included if they were performing any of these activities regularly for at least 30 minutes.

Statistical Analysis

The Statistical Package for Social Sciences (version 25.0) was used for the statistical analysis. The distribution of quantitative variables was evaluated by the Kolmogorov-Smirnov test. Statistics of quantitative variables are shown as the median (25^{th} to 75^{th} percentile), and the groups were compared with the Mann-Whitney U test if not normally distributed. Descriptive statistics of these variables are expressed as a frequency. Categorical variables are given as number and percentage, and chi-squared analyses were carried out. The binary logistic regression model was used to evaluate the contribution to the likelihood of hospitalization. All statistical significance was set at $p<0.05$.

Results

Sample Characteristics

The sample of this study consisted of 119 (n=85 in OP-ASD; n=34 in IP-ASD) cases. The individual, educational and familial characteristics of the groups are presented in Table I and Table II. The presence of psychopathology

Table I. Individual and educational characteristics of outpatient and inpatient ASD groups

	Outpatient ASD (n=85)	Inpatient ASD (n=34)	Statistic
Gender n (%) Female Male	 15 (17.6) 70 (82.4)	 7 (20.6) 27 (79.4)	χ^2: 0.139 df: 1 p=0.709
Age (median score)	12 (10-15)	12.5 (9-15)	*Z: -0.804 p value=0.421
Education status n (%) Formal education Special-education class No education	 46 (54.1) 30 (35.3) 9 (10.6)	 19 (55.9) 7 (20.6) 8 (23.5)	χ^2: 4.550 df: 2 p=0.103

Table I. Continued

	Outpatient ASD (n=85)	Inpatient ASD (n=34)	Statistic
Special education n (%)	73 (85.9%)	29 (85.3%)	χ^2: 0.007 df: 2 p=0.934
Intellectual/developmental functioning n (%) Normal Border Mild Moderate Severe	 24 (28.2%) 3 (3.5%) 18 (21.2%) 17 (20%) 23 (27.1%)	 7 (20.6%) 1 (2.9%) 18 (52.9%) 5 (14.7%) 3 (8.8%)	 χ^2: 12.734 df: 4 **p=0.013**

χ^2: Comparison of categorical variables was checked using chi-square analysis. *Mann-Whitney U test, bold value mark statistically significant differences.
ASD: Autism spectrum disorder

Table II. Familial characteristics of the outpatient and inpatient ASD groups

	Outpatient ASD (n=85)	Inpatient ASD (n=34)	Statistic
Mothers' age (median, min-max)	40 (37-43)	38.5 (35-46)	*Z: -0.197 p=0.844
Mothers' education years (median, min-max)	11 (0-15)	8 (0-15)	*Z: -2.394 **p=0.017**
Mother's employment n (%) Unemployed Working	 61 (71.8) 24 (28.2)	 22 (64.7) 12 (35.3)	 χ^2: 3.463 df: 4 p=0.484
Mother's psychiatric disorder n (%)	8 (9)	21 (61.8)	χ^2: 36.115 df: 0 **p<0.001**
Father's age (median, min-max)	45 (40.5-49)	44 (38.75-51.25)	*Z: -0.259 p=0.795
Fathers' education years (median, min-max)	11 (0-15)	11 (0-15)	*Z: -0.304 p=0.761
Father's employment n (%) Unemployed Working	 2 (2.4) 83 (97.6)	 0 34 (100)	 χ^2: 11.028 df: 5 p=0.51
Father's psychiatric disorder n (%)	2 (2.4)	8 (23.5)	χ^2: 14.149 df: 0 **p<0.001**
Sibling's psychiatric disorder n (%)	9 (10.6)	9 (26.5)	χ^2: 4.772 df: 1 **p=0.029**

χ^2: Comparison of categorical variables was checked using chi-square analysis, *Mann-Whitney U test, bold values mark statistically significant differences.
ASD: Autism spectrum disorder, min-max: Minimum-maximum

in the family was significantly higher in the IP-ASD group (mother psychopathology: χ^2=36.115; df=1; p<0.001, father psychopathology: χ^2=14.149; df=1; p<0.001, sibling psychopathology: χ^2=4.772; df=1; p=0.029) than in the OP-ASD group.

The rate of comorbid psychopathology was significantly higher in the IP-ASD group (χ^2=8.238; df=1; p=0.004). When we compared the CARS scores, the CARS median value was 36 (27.75-45) in the OP-ASD group, and it was 44 (35.75-52) in the IP-ASD group (Z score=-3.143, p=0.002). The comparison of clinical characteristics is presented in Table III.

Logistic Regression

The factors associated with hospitalization of ASD cases were demonstrated with the binary logistic regression analysis model (Table IV). The presence of psychopathology in the mother was found to be the factor which was associated with hospitalization (OR=10.293, p<0.001).

Table III. Comparison of clinical characteristics between the groups

	Outpatient ASD (n=85)	Inpatient ASD (n=34)	Statistic
Comorbid psychopathology n (%)	59 (69.4)	32 (94.1)	
ADHD	51 (60)	20 (58.8)	
ADs	10 (11.8)	1 (2.9)	χ^2: 8.238 df: 1
OCD	3 (3.5)	2 (5.9)	**p=0.04**
Conduct disorder	6 (7.1)	5 (14.7)	
MDD	2 (2.4)	2 (5.9)	
BPD	1 (1.2)	2 (5.9)	
Psychotic disorder	0	2 (5.9)	
Psychotropic medication use n (%)			
Atypical antipsychotic	64 (75.3)	34 (100)	
Risperidone	35 (41.2)	23 (67.6)	
Olanzapine	5 (5.9)	6 (17.6)	
Aripiprazole	23 (27.1)	15 (44.1)	
Quetiapine	1 (1.2)	3 (8.8)	
Clozapine	0	1 (2.9)	
Typical antipsychotics	6 (7.1)	12 (35.3)	
SSRIs			
Escitalopram	2 (2.4)	9 (26.5)	χ^2: 10.200 df: 1
Sertraline	8 (9.4)	3 (8.8)	**p=0.01**
Fluoxetine	4 (4.7)	1 (2.9)	
Fluvoxamine	0	1 (2.9)	
Stimulants	23 (27.1)	8 (23.5)	
Atomoxetine	10 (11.8)	9 (26.5)	
Mood stabilizer	2 (2.4)	12 (35.3)	
Benzodiazepines	0	14 (41.2)	
Anticholinergic	1 (1.2)	8 (23.5)	
Melatonin	1 (1.2)	4 (11.8)	
Number of drugs used n (%)			
No drug used	21 (24.8)	0	
Single drug used	24 (28.2)	2 (5.9)	*Z: -6.915
Dual drug used	28 (32.9)	1 (2.9)	**p value: <0.001**
Use of three or more drugs	12 (14.1)	31 (91.2)	
Medical comorbidity n (%)	13 (15.3)	8 (23.5)	χ^2: 1.133 df: 1 p=0.287
Exercising regularly n (%)	33 (38.8)	4 (11.8)	χ^2: 8.299 df: 1 **p=0.04**
CARS groups n (%)			
15-29	23 (27.1)	4 (11.8)	
30-36	24 (28.2)	7 (20.6)	χ^2: 5.542 df: 2 p=0.063
37-60	38 (44.7)	23 (67.6)	
CARS score (median, min-max)	36 (27.75-45)	44 (35.75-52)	*Z: -3.143 **p=0.002**

χ^2: Comparison of categorical variables was checked using chi-square analysis, *Mann-Whitney U test, p: p value, bold values mark statistically significant differences. ADHD: Attention-deficit/hyperactivity disorder, ADs: Anxiety disorders, OCD: Obsessive-compulsive disorder, MDD: Major depressive disorder, BD: Bipolar disorder, CARS: Childhood Autism Rating Scale, SSRIs: Selective serotonin reuptake inhibitors, min-max: Minimum-maximum

Table IV. Results of binary logistic regression model showing the likelihood of psychiatric hospitalization and relationship between associated factors

	β	OR	95% CI	p value
Comorbid psychiatric disorder	1.497	4.467	0.686-29.077	0.117
Presence of mild intellectual disability	-0.454	0.635	0.176-2.289	0.488
Psychopathology of the mother	2.332	10.293	3.479-30.452	<0.001
Psychopathology of the father	1.640	5.155	0.848-31.356	0.075
Psychopathology of the sibling	0.859	2.362	0.657-8.490	0.188

β: Estimate, OR: Odds ratio, CI: Confidence interval

Discussion

In this study, the OP-ASD group and the IP-ASD group were compared in terms of their individual, familial and clinical characteristics. According to the findings, although there was no significant difference between the age, gender, and educational status of the cases, it was observed that mild intellectual functioning was more associated with the hospitalization of patients with ASD. The rate of individual and familial psychopathology and medication usage of the inpatients was higher. Also, it was observed that the presence of psychopathology in the mother was a factor associated with hospitalization. Although there was no significant difference between the groups in terms of the presence of medical illness and participation in special education, it was observed that a history of participation in sports was higher in the OP-ASD group. In addition, when the two groups were compared in terms of the severity of their autism, it was determined that the autism severity scores of the IP-ASD group were higher than the OP-ASD group.

Symptom Severity and Comorbid Psychopathology of ASD Cases

The CARS scores of the IP-ASD group were found to be significantly higher. We thought that greater ASD severity necessitates intensive medical and hospitalization support, such as intensive and frequent school support (26). Taylor et al. (27) compared patients with ASD hospitalized in specialized and general psychiatry services using the Aberrant Behavior Checklist (ABC) and the ABC scores were found to be significantly higher in the specialized psychiatry service before hospitalization. Jang and Matson (28) showed that more severe symptoms of ASD were associated with more severe comorbid psychopathology. In our study, comorbid psychopathology, CARS scores and multiple psychotropic medication use were found to be significantly higher in the inpatient group.

In our study, comorbid psychopathology rates were significantly higher in the IP-ASD group than the OP-ASD group (94.1% vs 69.4%). Comorbid psychopathology diagnosis groups and rates in the OP-ASD group were consistent with literature (7-11). Righi et al. (18) reported that mood disorders and sleep problems were found to be higher in the inpatient group and showed that the presence of a mood disorder was the strongest predictor of hospitalization. In accordance with the literature, comorbid psychopathology was found to be significantly higher and mood disorders, psychotic disorder and conduct disorder were more common in the IP-ASD group. In our study, the use of psychotropic drugs was also found to be significantly higher in the inpatient group and this was also consistent with the literature findings (15,28). The symptom severity and higher comorbid psychopathology rates could have increased the medication rates. In line with our results, Mayes et al. (29) stated that more severely impaired children were more often medicated regardless of diagnosis. Additionally, many studies including cases with ASD have shown that psychotropic medication use increased with the presence of comorbid conditions such as ADHD, mood disorders, conduct disorders, aggression and ID (15,30,31).

In studies investigating risk factors associated with hospitalization in ASD, accompanying ID was found to be higher in the inpatient group (15,18). The accompanying severe ID in the OP-ASD group may lead to receiving diagnosis earlier. Children diagnosed with an ID were diagnosed with ASD 23 months earlier, and earlier diagnosis leads to accurate earlier intervention increasing adaptive functioning, decreasing challenging behaviors and is associated with more effective outcomes (32,33). As stated, ASD severity was lower in the OP-ASD group. These factors may be associated with hospitalization, in addition to the small sample size of the IP-ASD group.

This study detected that medical comorbidities did not differ significantly between the groups. In a study conducted by Righi et al. (18), the inpatient and outpatient groups were compared in terms of sleep problems, seizure history, dental problems, endocrine problems and gastrointestinal problems. In their study, the presence of sleep problems was found to be a predictor for hospitalization, but no significant difference was found in terms of the other factors. Similarly, there was no relationship between medical comorbidities and psychiatric hospitalization in our study. Also, regular participation in sports was found to be lower in the IP-ASD group. It can be said that participation and adaptation of sport activities were difficult due to the higher severity of ASD, and comorbid psychopathology in the IP-ASD group. There are also publications reporting a decrease in behavioral problems of those who can continue to exercise regularly (34,35).

Psychopathology of Parents

In the literature, many factors related to the hospitalization of children and adolescents diagnosed with ASD have been discussed, but there is no study investigating parental psychopathology and education levels. It is known that neurological and psychiatric diseases are more common in those families of children and adolescents diagnosed with ASD (36). Parental psychopathology is also known to be

a risk factor for psychiatric morbidity in children (37). In addition, in a study comparing adolescents between the ages of 13 and 17 in terms of their hospitalization history, it was shown that the presence of psychopathology in the mother was higher in adolescents with a hospitalization history, regardless of ASD diagnosis (38). However, the parents of children with ASD often endure more stressors than the caregivers of typically developing children, and so are at risk of experiencing increased risks for mental health problems (39-41). The level of parental stress is associated with child irritability, and the severity of the child's behavioral problems may predict psychopathology in the parents (42,43). In our opinion, this relationship can be bi-directional. The psychopathology and low education of mothers may affect ability to cope with the difficulties and find solutions for those children with neurodevelopmental difficulties. This may lead to the need for hospitalization in this group with high rates of psychiatric comorbidity. Although studies report different results, the importance of the parents' psychoeducation and participation in the treatment of ASD youth is mentioned (44,45). It is clear that the well-being and mental health of the parents are considerably important. Therefore, creating treatment models which include psychosocial support systems and providing consultancy services to families for preventive healthcare would be beneficial in the treatment of children and adolescents with ASD in order to reduce the risk of hospitalization, especially in developing countries.

Study Limitations

Similar to increasing prevalence rates, an increase has been reported in psychiatric hospitalization in children with ASD, but studies on the relevant factors associated with hospitalization are limited. The small sample size of IP-ASD cases is a limitation and restricts the generalizability of our data. Also, being based on self-report may mean that our results are subject to response bias. However, this was the first study from Turkey on IP-ASD cases. Therefore, studies with more cases are needed. In addition, the findings would be stronger if structured psychiatric interviews had been carried out with the parents.

Conclusion

The need for studies assessing individual characteristics such as disease severity, comorbid psychiatric disorders and medical illnesses, medication profiles, intellectual functioning, and education level, alongside familial factors such as psychopathology in siblings and parents, as well as parental age, has been reiterated in the literature concerning hospitalization in patients with ASD from various perspectives. Knowing which factors accompany those patients who are more associated with hospitalization may provide useful preliminary data to clinicians and mental health professionals. As the practice parameters of the American Academy of Child and Adolescent Psychiatry stated, the clinician should maintain an active role in the long-term treatment planning and as part of this long-term engagement, the parents and siblings of children with ASD will need support in addition to the support for the individual with ASD (46). In addition to outpatient family support, as the mother's well-being may be related to the severity of ASD in the child, we thought that it is also very important to have a team providing psychosocial support especially to the mothers during the treatment process.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Ege University Faculty of Medicine Clinical Research Ethics Committee (approval no: 20-7.1T/13, date: 22.07.2020).

Informed Consent: Parents and participants were verbally informed on the aim of the study, and written informed consent was obtained from parents in accordance with the Declaration of Helsinki.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: S.K., N.D., İ.B., B.Ü., E.T., Design: S.K., N.D., İ.B., B.Ü., E.T., Data Collection or Processing: S.K., N.D., İ.B., B.Ü., E.T., Analysis or Interpretation: S.K., N.D., İ.B., B.Ü., E.T., Literature Search: S.K., B.O., N.D., İ.B., Writing: S.K., B.O., N.D., İ.B., B.Ü., E.T.

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Case Report

A Novel Missense Variant c.125G>A on Exon 3-Presenting as Neonatal Purpura Fulminans with Persisting Fetal Vasculature

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ABSTRACT

Neonatal purpura fulminans due to severe congenital protein C deficiency is a rare autosomal recessive disorder which can be fatal if untreated. Here, we discuss a case report of a 10-month-old male child, born via 3rd degree consanguineous marriage, with a history of tractional retinal detachment and persistent fetal vasculature (PFV) now presenting with neonatal purpura fulminans and DIC who was managed with fresh frozen plasma (FFP) and Low Molecular Weight Heparin (LMWH). Genetic evaluation identified a novel PROC mutation c.125G>A(p.Arg42His). This report also emphasizes the significance of molecular analysis in genetic counselling and prenatal diagnosis.

Keywords: PROC, purpura fulminans, persisting fetal vasculature, newborn

Introduction

Neonatal purpura fulminans describe a clinicopathological entity of dermal microvascular thrombosis associated with disseminated intravascular coagulation (DIC). Neonatal purpura fulminans associated with congenital protein C deficiency is an exceedingly rare condition with a predicted incidence of 1 per 4 million births (1).

Biallelic (homozygous or compound heterozygous) PROC mutations lead to autosomal recessive Protein C Deficiency which occurs in 1 in 40,000 to 250,000 individuals. Autosomal recessive protein C deficiency, which is a more severe but rarer form compared to autosomal dominant protein C deficiency, is associated with a very low level of protein C and typically presents in the neonatal period with neonatal purpura fulminans (2).

Herein, we describe an infant who presented with neonatal purpura fulminans with retinal detachment secondary to persistent fetal vasculature and was found to have autosomal recessive protein C deficiency caused by a novel homozygous PROC mutation.

Case Report

A 10-month-old male child with normal development, born via 3rd-degree consanguineous marriage, with a family history of recurrent abortion in his maternal grandmother, presented to our center with a history of bluish discoloration of the left lower limb for 3 months following trivial trauma. The child had a history of similar episodes in the neonatal period on postnatal day 3, and it healed by 1 month of age. At 6 months of age, the mother noticed white reflex in the right eye and on evaluation, it was found that the child had

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leukocoria and complete vision loss in the right eye due to tractional retinal detachment caused by persistent fetal vasculature. Over a one-week period, the lesion progressed - became edematous, tender and there was oozing of serous fluid. The child was admitted, and on examination had a black eschar on the left lower limb, with a few vesicles and surrounding erythema (Figure 1). Ecthyma gangrenosum was suspected, and treatment was started with ceftazidime and vancomycin, along with other supportive measures. Initial investigations were unremarkable except for a marginally positive C-reactive protein. However, on the following day, the child worsened clinically, with the spreading of the lesions, new lesions in the scrotum and forehead, and the child appeared pale. Further investigation revealed anemia (Hb: 7.4 g/dL, reference range 11-13 mg/dL), thrombocytopenia (platelet count: 77×10^9/L, reference range 150-450$\times10^9$/L), elevated INR: 5 (reference range 0.9-1.2), elevated APTT: 70 seconds (reference range 24-36 seconds), elevated D-dimer: 8.9 mg/L (reference range <0.5 mg/L) and low fibrinogen: 76 mg/dL (reference range 180-410 mg/dL), suggestive of a child going into DIC.

In light of the family history of recurrent abortions, consanguineous marriage, similar past history, skin lesions similar to neonatal purpura fulminans, and the presentation in DIC, inherited thrombophilia including Protein C/Protein S deficiency was suspected. Protein C level assay was performed and was found to be low (Protein C level: 8 IU/dL, reference range for <5 years: 40-92 IU/dL). The child was started on fresh frozen plasma (FFP). Low molecular weight heparin was started at a dose of 1 mg/kg for 2 weeks and later bridged to warfarin. Escharotomy was carried out after 1 month. Following discharge, the patient returned to his usual state of health and has continued prophylactic LMWH. The PROC gene was sequenced and a novel homozygous missense mutation (c.125G>A; p.Arg42His) on Exon 3 was identified. A genetic study of both the parents was carried out and both were heterozygous for p.Arg42His mutation, confirming the diagnosis of autosomal recessive protein C deficiency.

Discussion

Protein C is a vitamin K-dependent serine protease anticoagulant which plays a critical role in the regulation of thrombosis by degrading activated procoagulant factors V and VIII (3). PROC, the gene encoding protein C, is located on chromosome 2q14.3 (4). Individuals with autosomal recessive protein C deficiency carry biallelic PROC mutations and have a very low level of protein C, whereas individuals carrying heterozygous PROC mutations have protein C levels at about 50% of reference values (2).

Neonatal purpura fulminans due to congenital protein C deficiency usually present within hours of birth with rapidly progressive cutaneous purpuric lesions and DIC. Most affected infants present with blindness and prenatal arterial ischemic stroke resulting from thrombosis in the developing vitreous vein. Douglas et al. (5) identified 12 cases where severe protein C deficiency was associated with ophthalmic signs compatible with a diagnosis of persistent fetal vasculature. The identified PROC novel mutation c.125G>A(p.Arg42His) had not been previously reported. This p.Arg42His variant has an allele frequency of 0.00079% in the gnomAD and is novel in the 1000 genome database. The amino acid arginine at position 42 is changed to histidine, changing the protein sequence and it might alter its composition and physicochemical properties (6).

The classic presentation of autosomal recessive protein C deficiency is often neonatal purpura fulminans and early recognition is critical in preventing morbidity and mortality. Although the identified p.Arg42His mutation in PROC was not previously reported, its pathogenicity is supported by biochemical and clinical phenotypes which are consistent with autosomal recessive protein C deficiency. Therefore, p.Arg42His in PROC is a novel mutation causing autosomal recessive protein C deficiency which presented in this infant

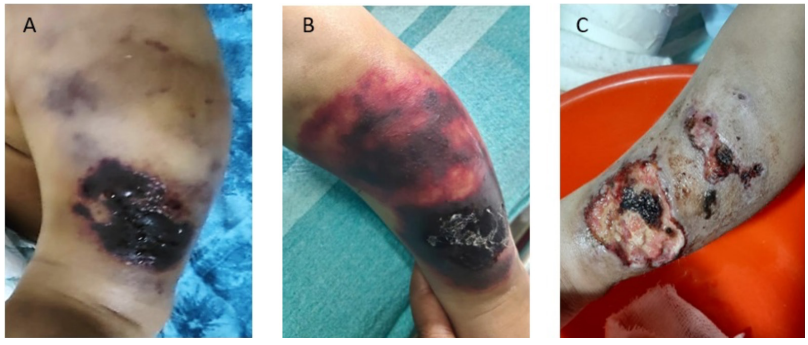

Figure 1. Skin changes at various stages: (A) At presentation in our hospital; (B) After progression into DIC; (C) After escharotomy

with neonatal purpura fulminans along with persistent fetal vasculature. This report also emphasizes the significance of molecular analysis in genetic counselling and prenatal diagnosis.

Ethics

Informed Consent: Obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.B., R.I., S.H., Concept: R.I., Design: S.H., Data Collection or Processing: A.B., Analysis or Interpretation: R.I., S.H., Literature Search: A.B., Writing: A.B.

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