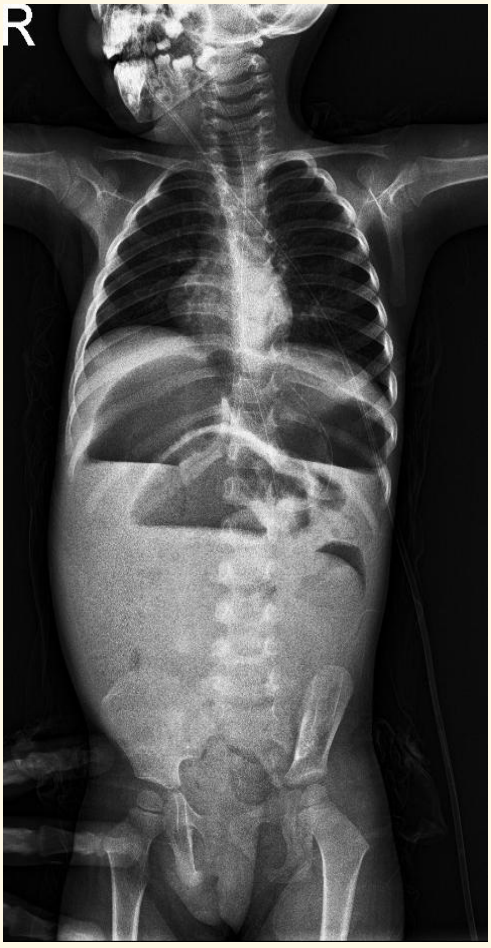
Year: December 2021 Volume: 8 Issue: 4

ISSN: 2147-9445
E-ISSN: 2587-2478

The Journal of Pediatric Research



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Phone: +90 (212) 429 10 00 | **Certificate Number:** 42419
Printing Date: December 2021
ISSN: 2147-9445 **E-ISSN:** 2587-2478
International scientific journal published quarterly.

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PRISMA statement of preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/);

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al., for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org/);

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Editorial

"You never fail until you stop trying."

Albert Einstein

Dear JPR readers,

We are currently going through a period in which vaccination and researches on COVID-19 pandemic are offering hope to the whole world. In this period, we are grateful to all scientists who contribute to science with outstanding success and to all healthcare professionals for their altruistic service.

We are pleased to share with you the 4th issue of The Journal of Pediatric Research of 2021. This issue consists of 24 valuable studies of which 19 are research articles and 5 are case reports. In this issue, we hope that you will be interested in reading the studies that evaluate the impact of COVID-19 on the health and diseases of children as well as the studies and case reports that comprise various subjects from several pediatric disciplines such as acute allograft dysfunction, antiepileptic drug and thyroid functions, percutaneous endoscopic gastrostomy, vesicoureteral reflux, polychlorobiphenyls and puberty precocious, food addiction and obesity, parents and circumcision, pediatric urethral strictures, vitamin D, FMF, reducing noise in neonatal intensive care unit, dental health and medical conditions, reproductive health education program and adolescents, hyponatremia in lower respiratory tract infection, fetal cardiac arrhythmia, orocutaneous fistula, congenital portosystemic shunt, insulin edema, colonic tubular duplication and hypovolemic shock.

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Best wishes,
Dr. Yeliz Çağan Appak

J Pediatr Res 2021;8(4):370-6
DOI: 10.4274/jpr.galenos.2020.98250

Original Article

The COVID-19 Pandemic and Enzyme Replacement Therapy in Lysosomal Storage Disorders

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ABSTRACT

Aim: The coronavirus disease-2019 (COVID-19) pandemic has caused a worldwide public health emergency, especially affecting people with chronic illnesses including lysosomal storage disorders (LSDs). The unfavorable conditions due to COVID-19 have mostly affected people with chronic conditions, in terms of disease vulnerability and access to health-care. In the present study, we aimed to assess the problems the patients with LSDs on enzyme replacement therapy (ERT) have encountered during the pandemic, and their level of anxiety. Parental evaluation has also been made for pediatric patients.

Materials and Methods: A total of 19 participants were recruited. A semi-structured interview was structured to evaluate the effects of the COVID-19 pandemic on ERT. The Turkish version of "Hospital Anxiety and Depression scale" (HADS) for adult patients and parents were used to evaluate anxiety. Patients between ages 8-17 completed the child version of the Revised Child Anxiety and Depression scale (RCADS).

Results: The study was completed by 19 patients, and 13 parents. Five patients (26%) admitted temporary disruption of treatment, of which the most common reason was the fear of getting infected. Eighty-nine percent of all participants were willing to receive treatment at home. Only one adult patient revealed to feel anxiety (16%). While among parents evaluated with HADS, 7/13 had scores that indicated depression and anxiety, 3/4 pediatric patients had RCADS scores indicative of anxiety and depression.

Conclusion: The problems LSD patients have been facing during the pandemic, should be identified along with their attitudes regarding ERT in order to maintain the sustainability of their treatment. The psychological health of these patients should also be identified and supported, to provide optimal care to patients.

Keywords: COVID-19, lysosomal storage disease, enzyme replacement therapy, home-therapy

Introduction

The coronavirus disease-2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has become a global problem, affecting nearly every country since March 2020 (1). Along with increasing cases and unavailability of a specific treatment, the health systems of countries have become overloaded with the burden of the pandemic. The disease has caused increased anxiety worldwide, also in children, due to the fear of getting infected, and suffer its severe complications.

The unfavorable conditions due to COVID-19 have mostly affected people with chronic conditions, in terms of disease vulnerability and access to health-care (2). Patients who

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Received: *07.10.2020* **Accepted:** *16.11.2020*

are dependent on health-care facilities on a routine basis, have faced several problems due to restrictions concerning treatment and follow-up visits, since most of the hospitals have been focused on the treatment of the patients severely affected with SARS-CoV-2. Also, due to the fact that these patients are obliged to attend health-care facilities, the risk to get infected by the COVID-19 pandemic has increased (3).

People with rare metabolic disorders are also under risk during the pandemic because of multi-systemic involvement including vital organs (4). Lysosomal storage diseases (LSDs), are a group of rare, inherited metabolic disorders, that are characterized by progressive accumulation of non-digested substrates within cells, due to diminished activity of lysosomal enzymes. Although they cannot be cured, some treatment options have been emerged by the advances in the field. Enzyme replacement therapy (ERT) is administered as intravenous infusions, for every 1-2 weeks, and has been successful in many LSDs. Although hematopoietic stem cell transplantationand substrate reduction therapy (SRT) are available for a limited number of LSDs, ERT is the only approved and most effective therapy for the majority for now, and requires lifetime administration due to short half-life (5).

At the present time, Gaucher, Fabry, Pompe diseases, acid lipase deficiency, as well as mucopolysaccharidoses (MPSs) type I, II, VIa, VI and VII can be treated by ERT (Table I) (6). Although many centers provide the facilities for home-based infusions for these patients, in some countries patients need to attend hospitals to receive treatment, as in Turkey.

In the present study, we aimed to evaluate the problems regarding treatment of patients with LSDs on ERT during the COVID-19 pandemic. We have also assessed the anxiety levels of patients and parents related with the pandemic, using validated depression scales.

Materials and Methods

The study was carried on between September and October 2020. Patients with LSDs that were receiving ERT in University of Health Sciences Turkey, Dr. Sami Ulus Maternity and Child Health Training and Research Hospital were invited to participate in the study. A semi-structured interview was designed on the attitudes of patients or their parents regarding the COVID-19 pandemic. Also, the difficulties that the patients experienced during hospital admission and access to medication were evaluated. Parents were asked to complete a set of questions including age, sex, duration of ERT, the presence of COVID-19 infection within the family or relatives, contact with a COVID-19 patient, adherence to the restrictions due to the pandemic, and any problems encountered during hospital admissions for ERT or access to medications (Table II).

To assess depressive symptoms of patients between ages 7-18, Revised Children's Anxiety and Depression scale (RCADS), and patients above the age 18, and for parental evaluation, the "Hospital Anxiety and Depression scale" (HADS) were used. Both of these questionnaires have been shown to be a reliable and valid tool to assess the general population (7).

The RCADS consists of 47 items developed to evaluate DSM-IV based symptoms of anxiety disorders and depression in children and adolescents, and their parents, with response options of 0= never, 1=sometimes, 2=often, and 3=always (7). The questionnaire was validated in Turkish by Gormez et al. (8,9). The answers of the questionnaire are grouped into six subscales: Separation Anxiety Disorder, Anxiety Disorder (General Anxiety Disorder), Social Phobia, Panic Disorder, Major Depressive Disorder, and Obsessive Compulsive Disorder. For each subscale, scores are given, as well as a total anxiety score, which is the sum of all anxiety, and a total score for all the scales (sum of six subscales). Higher score indicates greater depressive symptoms. Raw scores are converted to age and gender adjusted T scores, using standardized tools (7).

Table I. ERTs available for various LSDs

LSD subtype	ERT
Gaucher disease	Imiglucerase Taliglucerase Velaglucerasa alfa
Fabry disease	Agalsidase alpha Agalsidase beta Pegunigalsidase alpha
MPS I (Hurler-Scheie syndrome)	Laronidase
MPS II (Hunter syndrome)	Idursulfase Idursulfase beta
MPS IVa (Morquio A syndrome)	Elosulfase alpha
MPS VI (Maroteaux-Lamy syndrome)	Galsulfase
MPS VII (Sly syndrome)	Vestronidase alpha
Acid lipase deficiency	Sebelipase alpha
Pompe disease	Alglucsidase alpha
Alpha-mannosidosis	Velmanase alpha

ERT: Enzyme replacement therapy, LSD: Lysosomal storage disorders, MPS: Mucopolysaccharidose

Table II. Questions of the semi-structured interview on the attitudes of patients regarding ERT during the pandemic
Age:
Sex:
Patient Parent
Diagnosis:
Duration of ERT: ..... years
Have you or your child been diagnosed to be infected with COVID-19? Yes ❒ No ❒
Have you felt anxiety regarding the COVID-19 pandemic? Yes ❒ No ❒
Have you adhered to the restrictions regarding the COVID-19 pandemic? Yes ❒ No ❒
Have you (or your child) had any interruptions of enzyme replacement therapy during the COVID-19 pandemic? Yes ❒ No ❒
Have you ever felt anxiety during at the hospital during receiving enzyme replacement therapy regarding the COVID-19 pandemic? Yes ❒ No ❒
Have you ever felt anxiety during transportation to hospital for enzyme replacement therapy regarding the COVID-19 pandemic? Yes ❒ No ❒
Have you ever felt anxiety during attending pharmacies for drug supply regarding the COVID-19 pandemic? Yes ❒ No ❒
Did you have any treatment interruptions during the COVID-19 pandemic? Yes ❒ No ❒ If so, which of the following items describes the reason for treatment interruption? a) Fear for myself (or my child) to get infected at the hospital b) Fear for myself (or my child) to get infected during transport to hospital due to using public transportation c)The hospital I / my child is receiving therapy are too occuppied with COVID-19 patients
COVID-19: Coronavirus disease-2019, ERT: Enzyme replacement therapy

Hospital Anxiety and Depression scale (HADS) consists of 14 items divided into two subscales for anxiety and depression (7 depressive and 7 anxiety items). The items are rated on a 0-3 scale, where each items are summed to reach a total score. A score of ≥10 indicates anxiety, where ≥7 indicates depression (10). It is validated to be used in adolescents, and has suitable psychometric properties for this population (11).

The questionnaires were conducted in a private room by patients and parents and took about 5 minutes to complete. Patients that did not attend our clinic during the study period completed the survey via telephone. All participants provided informed consent.

Ethics approval was obtained from the ethics committee of Ankara Yıldırım Beyazıt University, on September 2020, from the local institutional review board according to guidelines of the Helsinki Declaration of Human Rights.

Results

At the time of the study, 22 LSD patients being followed-up in our department, were on ERT, and thus regularly admitted to the outpatient clinic, 19 of whom accepted to participate in the study. The study was completed with 19 patients (13 pediatric and 6 adult patients) and 13 parents.

The ages of pediatric patients at ranged from 2.5 to 16 years (mean age: 7.7±4.7 years). Male to female ratio was (7/6). Ages of adult patients ranged from 19 to 50 years (mean age: 35.2±14.1) (male to female ratio: 4/2). Thirteen parents were also evaluated, ages ranging between 27 and 44 years (mean age 33.8±5.98), and male to female ratio being 4/9. The demographic data of patients are given in Table III. All patients were receiving ERT (alglucosidase alfa, laronidase, idursulfase, galsulfase, imiglucerase, taliglucerase alfa, agalsidase alfa, oragalsidase beta, according to diagnosis). The patients were receiving ERT for 1 to 14 years. Mean duration of ERT was 4.5±3.2 years (Table III).

None of the patients had a proven diagnosis of an infection with COVID-19. All patients indicated that they complied with the precautions that were being taken by the ministry of health. Three patients revealed getting into contact with a person diagnosed with COVID-19 from relatives, but had no signs of infection.

Five patients (26%) admitted temporary disruption of treatment. Four of these patients were continuing ERT at longer intervals (once a month). The most common reason was the fear of getting infected at the hospital, or during transport to hospital due to using public transportation. One patient had missed one infusion on March 2020, due to inadequacy of hospital services dealing with the burden of COVID-19 (Table IV). Eighty-nine percent of participants were willing to receive their treatment at home during the pandemic, other than two patients, one the parent of a child

Table III. Demographic characteristics of patients enrolled in the study

Demographic characteristics	Patients	Parents
Age (mean ± SD)		
Pediatric	2.5-16 years (7.7±4.7 years)	
Adult	19-50 years (35.2±14.1)	27-44 years (33.8±5.98)
Sex		
Pediatric		
Male	7	
Female	6	
Adult		
Male	4	4
Female	2	9
Duration of ERT (mean ± SD)	4.5±3.2 years	
Subtype of LSD (n)		
Fabry disease	6	
Gaucher diasease	3	
MPS 1	2	
MPS 2	2	
MPS 6	2	
Pompe disease	4	

ERT: Enzyme replacement therapy, LSD: Lysosomal storage disorders, MPS: Mucopolysaccharidose, SD: Standard deviation

Table IV. The reasons of distruption of treatment

Reason of distruption	(n)
Fear of getting infected at the hospital	4
Fear of getting infected during transport to hospital	4
Hospital services loaded with the burden of COVID-19	1

COVID-19: Coronavirus disease-2019

with Pompe disease who had a history of anaphylaxis during treatment and an adult Fabry patient due to a personal feeling (fear of allergic reaction).

Nine out of thirteen parents claimed to feel anxiety during hospital admissions or regarding drug supply (69%), among them, 7 (53%) had HADS scores that indicated depression, and increased anxiety. Among the children of these parents, 3 had interrupted treatment during the pandemic, and the reason for interruption was the fear of getting an infection (Table V).

Table V. Anxiety and depression levels of patients and rate of treatment interruption

	Positive* (n)	Interruption of treatment among participants with increased anxiety and depression (n)
Claim of feeling anixety during hospital admission for ERT		
Patients		
Adult	1/6	1
Pediatric	2/4	
Parents	9/13	
HADS score		
Adult patients	1/6	1
Parents	7/13	3**
RCADS score		
Patients (Aged 8-17)	3/4	2

*Indicating anxiety and depression
**Indicates treatment interruption of children of these parents
ERT: Enzyme replacement therapy, RCADS: Revised Child Anxiety and Depression Scale

Among 6 adult patients, only one (who is also the mother of one pediatric patient) had scores indicative of anxiety and depression, who had also interrupted treatment. The same patient revealed to feel anxiety of getting infected during hospital admissions or at pharmacies (16%).

Among patients aged 8-17 that were evaluated by RCADS (4 patients), sub-scores of 3 patients (75%) were found to be above the threshold level and one of these 3 patients also had high total anxiety and depression scores. Two of these patients had also interrupted treatment due to fear of getting infected during receiving ERT.

Statistical Analysis

Statistical analyses regarding the relationship between interruption of treatment and anxiety scores were not performed due to insufficient number of patients enrolled in the study.

Discussion

The COVID-19 pandemic due to SARS-CoV-2 caused weaknesses in the world-healthcare systems of countries, pre dominating rare and chronic conditions including inborn errors of metabolism (1,2). Particularly, patients with inborn errors of metabolism (IEMs) can be considered at high risk for severe SARS-CoV-2 infection, since they often suffer

from a multisystem disease, including respiratory and cardiovascular system involvement (12).

It is well known that SARS-CoV-2 uses the lysosomal system to infect cells (13). Therefore, patients with LSD may be at increased risk for infection and complications of SARS-CoV-2, because of lysosomal dysfunction, and activation of inflammatory cascades (14).

Our study group consists of a vulnerable population, not only due to the effects of the disease itself, but also being dependent on health-care services in terms of treatment. Neither of our patients had a proven diagnosis of COVID-19. This may be due to the strict adherence of patients to the rules for prevention of infection. It is impossible to generalize our findings, since tests were not done on a routine basis, and asymptomatic cases could not be ruled out. Previous studies reported in the literature have also reported low incidence of COVID-19 among LSD patients (12,15).

Scarce amount of studies exist in the literature addressing LSD patients during the COVID-19 pandemic. Mistry et al. (14) have published guidelines for the management of Gaucher disease patients and have indicated that ERT should be continued regularly, and interruptions should not be extended, even in infected patients, to avoid aggravation of symptoms due to withdrawal of treatment and also support the vital organ systems, in case of infection. The authors have stated that, interruption of therapy for weeks to months could be tolerated in stable patients. Unfortunately, it is impossible to generalize these guidelines to other subtypes of LSDs, since each LSD is unique in its own clinical findings and progression.

A study by Andrade-Campos et al. (12) revealed that, among 48 Gaucher disease patients receiving hospital-based ERT, 11 (25%) reported therapy interruptions related with the outbreak, while patients on oral SRT continued to receive treatment regularly. Sechi et al. (16) have reported 102 patients with various types of LSDs, of whom 71 were receiving ERT during the pandemic. While, patients receiving home-based ERT continued their treatment regularly, disruptions occurred in 49% of patients receiving ERT in the health-care centers (16).

Unfortunately, home-therapy is not currently available in Turkey. Thus, all patients recruited in our study were on hospital-based treatment. The rate of interruption of treatment was 26% in our study, similar to the study reported by Andrade-Campos et al. (12). Obviously, our study population does not reflect the overall situation in our country. Turkey has been suffering from the devastating effects of the pandemic, and the rate of interruption of treatment among LSDs may be much higher.

In a recent report, Elmonem et al. (4) have analyzed 16 centers taking care of IEMs during the COVID-19 pandemic. According to their report, 88% of centers have limited the numbers of routine patients' visits per day and 20% of have referred patients to other IEM clinics. Also, travel restrictions have affected the follow-up of patients of 93% of participating centers. The authors have specified the most important factor of treatment interruption to be the fear of the patient and the family from going to the hospital during a pandemic, and have suggested clear guidelines for patient management in each subgroup of IEMs to be prepared in such circumstances (4).

Since ERT is given with frequent intervals (weekly or bi-weekly), the obligation to attend health-care facilities regularly, is not only time consuming, but also is unmanageable during times of overloading to the health-systems. Home therapy should be encouraged in patients with stable conditions as LSDs, since it is an efficient and comfortable way to sustain treatment during pandemics. Another solution may be separation of specific centers for the care of patients with rare and chronic illnesses to be infusion centers, or sparing a safe are within centers for infusion. Since a shortage of health-care staff may also be present during an emergency state, developing protocols for the management of LSDs during pandemics is also necessary. Also, to ensure safe transport of patients to health centers may be helpful.

Several studies have shown that the COVID-19 pandemic has led to panic and anxiety in patients with chronic illnesses (17). Fiumara et al (18) have specifically analyzed the attitude of 15 patients with LSD towards the pandemic and the impact of the outbreak on their treatment. Parents of patients at pediatric ages were also involved in the study. Although no statistically significant difference was found compared to controls, all the evaluated persons revealed increase of anxiety related with COVID-19. The authors concluded that, the reactions of patients with LSD were qualitatively different than the general population, and they have stressed the fragility and isolation of such patients.

Similar to the studies in the literature, we have also determined depressive symptoms in the majority of our study group consisting of LSD patients and their parents. What is more interesting was that, a considerable number of parents with anxiety and depression, had interrupted their child's treatment, with the fear of getting infected. The same situation was observed among the adult patients,

in which the patient with HADS scores indicative of both anxiety and depression, was the one who interrupted treatment. Our study indicates that, increased anxiety, along with depression, may aggravate the fear related with the pandemic, and may contribute to withdrawal of ERT. Thus, the identification of patients with anxiety and depression may be useful, since LSDs represent a vulnerable group of patients. Patient organizations may also be helpful, a part of care and support. The patients should be encouraged for the continuation of treatment.

Study Limitations

Our study has various limitations. First of all, a small number of patients were evaluated that may not reflect the whole population of LSDs that have been diagnosed and being treated in our country, and may not be generalized. Secondly, parental reports were evaluated for children under age 8 which may not directly reflect the child's own feelings.

Conclusion

Patients with LSDs represent a vulnerable group of the population due to the multisystemic effects of the disease. It is important to identify the problems these patients have been facing during the pandemic, also their attitudes regarding ERT in order to maintain the sustainability of their treatment. There is an urgent need to introduce home-based treatment options, where unavailable, to reduce the unfavourable health impacts due to disruptions of treatment. Also, individual guidelines for subtypes of LSDs should be created for the treatment strategies during the pandemic. Home-based therapy should be a choice for suitable patients since the effects of the pandemic seem to continue for an unpredictable period of time. The psychological health of these patients should also be identified, where needed, to provide optimal care to patients.

Ethics

Ethics Committee Approval: Ethics approval was obtained from the ethics committee of Yıldırım Beyazıt University, on September 2020 (number: 76).

Informed Consent: All participants provided informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.O., C.S.K, S.B.A., Y.Y., G.K.M., M.K., Concept: A.O., C.S.K, M.K., Design: A.O., C.S.K, M.K., Data Collection or Processing: A.O., S.B.A, Y.Y., G.K.M., Analysis or Interpretation: A.O., S.B.A., Y.Y., M.K., Literature Search: A.O., S.B.A, Y.Y., G.K.M., Writing: A.O., C.S.K, S.B.A., Y.Y., G.K.M., M.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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J Pediatr Res 2021;8(4):377-81
DOI: 10.4274/jpr.galenos.2020.15679

Original Article

Complications of Percutaneous Endoscopic Gastrostomy in Children: A Single Centre Experience

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ABSTRACT

Aim: The aim of this study was to investigate the complications of percutaneous endoscopic gastrostomy in children.

Materials and Methods: Ninety-one pediatric patients treated with percutaneous endoscopic gastrostomy (PEG) insertion by pull technique in a five-year period were enrolled into this study. Their hospital records were reviewed retrospectively for their demographic data, their primary diseases causing nutritional insufficiency, and any major or minor complications after PEG insertion.

Results: The 91 patients who were included in this study were aged between 1 month and 18 years (median 79 months). 45.1% (n=41) of the patients were female. The majority of the patients (76.9%, n=70) had neurological diseases. Nineteen patients (20.9%) had metabolic diseases and two patients had cystic fibrosis (2.2%). We observed 37 (40.7%) complications in total. Three (3.3%) of them were major and 34 (37.4%) of them were minor complications.

Conclusion: Endoscopic percutaneous gastrostomy placement is an important way to continue enteral feeding in children. Although PEG is a minimally invasive technique, there are some problems which may be experienced by the children and their parents after PEG insertion, the majority of the these being minor complications.

Keywords: Percutaneous endoscopic gastrostomy, complication, children

Introduction

Gastrostomy is used widely to enable enteral feeding in those patients who cannot intake enough nutrition orally for various reasons in the presence of a functional gastrointestinal system (1). Enteral feeding is cheaper than parenteral feeding. It also maintains gut functions, inhibits bacterial translocation and prevents complications of parenteral nutrition (2). Gastrostomy can be applied surgically (3) or endoscopically as first defined by Gauderer et al. (4) in 1980. The endoscopic technique, which is less invasive than the surgical technique, also prevents long-term hospital stays, causes less incisional pain and

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Received: *09.10.2020* **Accepted:** *28.12.2020*

allows for early feeding (1,5). Therefore, the percutaneous endoscopic gastrostomy (PEG) placement technique has become a commonly used method in pediatric patients and can be safely used by pediatric gastroenterologists even for small infants to enable enteral feeding (6).

This relatively minimal invasive method has some major and minor complications estimated to be between 4% and 44% (5,7-9). McSweeney and Smithers (6) reported the major and minor complication rates to be 10.5% and 16.5% respectively in their study on children in 2016. Lalanne et al. (9) reported 43% early and 56% late complications (85% of them were minor) (8).

The aim of this study was to investigate the complications of PEG in children in a tertiary center in Turkey.

Materials and Methods

This retrospective study was carried out in the Antalya Training and Research Hospital, Clinic of Pediatric Gastroenterology in Antalya, Turkey. All pediatric patients treated with PEG insertion by pull technique between June 2014 and May 2019 were enrolled in the study. Patients who underwent gastrostomy insertion surgically and those whose information could not be obtained from the hospital records were excluded from the study.

The hospital records were reviewed retrospectively for the demographic data of the patients, their primary diseases causing nutritional insufficiency and their major or minor complications after PEG insertion.

Gastric perforation, gastro-colic fistula, internal leakage, track dehiscence, peritonitis, periprocedural aspiration pneumonia, subcutaneous abscess, bleeding, gastric outlet obstruction, cellulites/necrotizing fasciitis, massive pneumoperitoneum, or buried bumper syndrome (internal fixation device migrates along with the tract of the stoma outside the stomach) were accepted as major complications and tube blockages, tube dislodgements, tube degradation, external leakage, unplanned removal, transient gastroparesis, gastric wall ulceration or site infections were accepted as minor complications (5).

The study was approved by the local ethics committee (Antalya Education and Research Hospital Ethics Committee of Clinical Investigations, no: 2019-155; date: 16th May, 2019).

Statistical Analysis

Statistical analysis was performed by SPSS 18.0 software package (SPSS Inc. Chicago, IL). Categorical variables were expressed as frequencies and percentage and numerical variables as mean/median (range). Shapiro-Wilk test was used to determine the normality of data distribution. The age of the patients was expressed as median because of the abnormal distribution by Shapiro-Wilk test.

Correlation analyses were evaluated with Spearman's correlation test. A p-value of less than 0.05 was considered to be statistically significant.

Results

Ninety-one patients were included in this study aged between 3 months and 18 years (median: 79.5 months). 45.1% (n=41) of the patients were female. The majority of the patients (76.9%, n=70) had swallowing dysfunction due to neurological diseases. The demographic characteristics and primary diseases of the patients are shown in Table I.

Table I. Demographics and primary diseases of our patients leading to their nutritional insufficiency

Demographics		
Age (months)	**Median**	79 (3-216)
Sex [n (%)]	**Female**	**41 (45.1%)**
Primary disease		**[n (%)]**
Neurological diseases		**70 (76.9%)**
	Cerebral palsy	54 (59.3)
	Sequela of traffic accident	4 (4.4)
	Hydrocephalus	3 (3.3)
	Hypoxia due to aspiration	2 (2.2)
	HIE*	2 (2.2)
	Spinal muscular atrophy	2 (2.2)
	Congenital muscular dystrophy	1 (1.1)
	Hypoxia due to status epilepticus	1 (1.1)
	Oncological disease	1 (1.1)
Metabolic diseases		**19 (20.9%)**
	Mitochondrial diseases	4 (4.4)
	MPS* type 1	3 (3.3)
	Tay-sacs disease	2 (2.2)
	Canavan disease	1 (1.1)
	Pompe disease	1 (1.1)
	Undiagnosed	8 (8.9)
Cystic fibrosis		2 (2.2)

HIE*: Hypoxic ischemic encephalopathy, MPS*: Mucopolysaccharidosis

The follow-up period of our patients varied from 6 months to 5 years (mean 2.34±2.45 year). Three of the patients (3.3%) had ventriculoperitoneal (V/P) shunt and one patient (1.1%) had intraabdominal baclofen pump.

Totally, 37 (40.7%) of the patients developed complications, three (3.3%) of which were major and 34 (37.4%) were minor complications. The major complications were intraabdominal abscess formation (n=1: 1.1%), buried bumper syndrome (n=1: 1.1%) and peritonitis (n=1: 1.1%) (Table II). Intraabdominal abscess was observed in the patient with intraabdominal baclofen pump. It was drained by needle aspiration by an interventional radiologist and antibiotic was applied intravenously for three weeks. Feeding through gastrostomy was initiated after two weeks. Buried bumper syndrome was observed in one patient and it was managed by surgical intervention. The patient with peritonitis was successfully treated with parenteral antibiotic for ten days.

Thirty-four (37.4%) minor complications were observed in our patients. Over granulation was seen in 14 patients (15.4%), tube blockage in 6 patients (6.6%), external leakage in 6 patients (6.6%), tube degradation in 4 patients (4.4%), and tube dislodgement in 4 patients (4.4%) (Table II).

The gastrostomy tube was removed completely in four patients. Three of these were due to sufficient nutritional intake (3.3%) (traffic accident patients n=2, status epilepticus patient n=1) and one of these was due to unmanaged skin lesion caused by leakage of gastric content.

The median time duration after PEG insertion and the occurrence of complications was 7 days (2 days-2 years) and 14 months (2-30 months) for major and minor complications respectively. There was no correlation between major or minor complications and time duration after PEG insertion ($p>0.05$ for both). There was also no correlation between age and complications ($p>0.05$).

Four of the patients (4.4%) died due to non-gastrostomy related causes during this 5-year period.

Discussion

In 91 patients, we observed 37 (40.7%) complications, 34 (37.4%) of which were minor complications.

Malnutrition is a very important health issue in growing children. Gastrostomy or, in special cases, enterostomy have been recommended by ESPGHAN for those children who cannot be fed by the oral route for more than 4-6 weeks (10). Gastrostomy placement improves the course of the underlying disease, nutritional status, and decreases hospital attendance and the time needed for feeding and it also increases the quality of life of the children and their caregivers (11-13). Percutaneous endoscopic gastrostomy placement has been the preferred method in children for a long time by pediatric endoscopists (14,15).

The majority of our patients had swallowing difficulties due to neurological problems (76.9%, n=70) followed by metabolic diseases (20.9%, n=19) and cystic fibrosis (2.2%, n=2). Neurological problems are also the leading cause of the PEG insertion in other studies (8,15-19).

Minor complications have been reported to be between 22% and 66.3% in the literature (1,19-24). In this study, we observed 34 (37.4%) minor complications, these were as follows; hypergranulation (n=14; 15.4%), peristomal leakage (n=6; 6.6%), tube blockage (n=6; 6.6%) or dislodgement (n=4; 4.4%).

Hypergranulation around the tube (15.4%) was the most common minor complication in our study. Hypergranulation with peristomal leakage are also the most reported minor complications in previous studies (5,15,25-30).

We observed 3 (3.3%) major complications which were intraabdominal abscess formation (n=1), peritonitis (n=1) and buried bumper syndrome (n=1). The major complication rate has been reported to be between 3.3% and 12.6% in the literature (1,19-24). Hansen et al. (19) and Khattak et al. (24) reported major complication rates of 2.6% and 3.3% respectively, which are similar to our major complication rate. Balogh reported a major complication rate of 10% with

Table II. Minor and major complications

Minor complications	**n (%)**	**Major complications**	**n (%)**
Over granulation	14 (15.4)	Intraabdominal abscess	1 (1.1)
Tube blockage	6 (6.6)	Peritonitis	1 (1.1)
External leakage	6 (6.6)	Buried bumper syndrome	1 (1.1)
Tube degradation	4 (4.4)		
Tube dislodgement	4 (4.4)		
Total	**34 (37.4%)**		**3 (3.3%)**

50% of these being related with infections (1). In the same study, buried bumper syndrome, intra-abdominal bleeding and ileus were reported in 1% of the patients (1). Our major complication rate was also comparable with their results with 2 thirds being related to infection.

The lower major complication rate in this study might be due to the fact that the majority of our patients (76.9%) were composed of neurologically impaired patients. As defined by McSweeney and Smithers (6) these patients are under supervision due to their special conditions, so lower complication rates were reported in this group.

Buried bumper syndrome was observed in one (1.1%) patient in this study at the end of the second year of PEG insertion. In the literature, 1.3% to 2.3% buried bumper syndrome rates have been reported, with these usually occurring in the second year (31,32).

Patients with V/P shunt have been reported to have a higher risk of complications (22,33). In their study, Fortunato et al. (8) reported higher complication rates in patients with V/P shunt and oncological diseases (8). We observed no complication in our patients with V/P shunt. This might be due to the low number of patients with V/P shunt in our study.

There was no correlation between age and complications in our study as defined previously by Szlagatys-Sidorkiewicz et al. (15).

Study Limitations

There are some limitations of our study; firstly, the relatively low number of cases in this study and secondly, since this is a retrospective study, some minor complications might not have been reported by the families. We recommend that further prospective studies with larger numbers of patients be carried out.

Conclusion

Endoscopic percutaneous gastrostomy placement is an important way to continue enteral feeding in children with various forms of inadequate nutritional intake. Although percutaneous endoscopic technique is minimally invasive, it has some complications, the majority of which are minor complications.

Ethics

Ethics Committee Approval: The study was approved by the local ethics committee (Antalya Training and Research Hospital Ethics Committee of Clinical Investigations, no: 2019-155; date: 16th May, 2019).

Informed Consent: Informed consent was obtained from all of the parents before the procedure.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.A.I., U.E.A., A.A., Y.B., H.S.K., Concept: İ.A.I., U.E.A., Y.B., H.S.K., Design: İ.A.I., U.E.A., Y.B., H.S.K., A.A., Data Collection or Processing: İ.A.I., U.E.A., Y.B., H.S.K., A.A., Analysis or Interpretation: İ.A.I., U.E.A., Y.B., H.S.K., A.A., Literature Search: İ.A.I., Writing: İ.A.I., U.E.A., A.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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J Pediatr Res 2021;8(4):382-8
DOI: 10.4274/jpr.galenos.2020.15985

Original Article

Etiological and Clinical Evaluations of Patients with Acute Allograft Dysfunction Within the First Year

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ABSTRACT

Aim: Kidney transplantation is the most preferred long-term treatment of children with end stage renal disease since 1954. Graft dysfunction has been divided into three categories based on timing of presentation. In this article, we aim to present the etiologic factors of acute graft dysfunction in the first year of renal transplantation in children.

Materials and Methods: The patients, diagnosed with acute allograft dysfunction in first year of kidney transplantation, in University of Health Sciences Turkey, Tepecik Training and Research Hospital between March 2005 and October 2017 were analyzed prospectively in this study.

Results: Over the 15 year period, 56 pediatric renal allograft patients were followed in University of Health Sciences Turkey, Tepecik Training and Research Hospital. During this period, 25 patients had diagnosed with early allograft dysfunction. Five patients were admitted two times in a year with allograft dysfunction. The mean age of patients was 12.6 (4.0±21.0) years, with a male and female ratio of 17:8. Delayed graft function was occurred in four patients (16%). Among 25 renal allograft recipients showed early graft dysfunction on average of 4.2 months (1-10 months) after transplantation. The etiology of early graft dysfunction showed 10% immunologic diseases and 90% non-immunologic factors. Five patients (16.7%) diagnosed with urinary tract infection, one patient (3.3%) diagnosed with cytomegalovirus nephropathy, five patients (16.7%) diagnosed with BK nephropathy, eight patients (26.7%) diagnosed with acute cyclosporine toxicity, seven patients (23.3%) were diagnosed with dehydration and one patient (3.3%) diagnosed with urologic anomalies. Twelve patients had performed renal allograft biopsy. The histological findings were consistent with T-cell mediated rejection in two patients; B-cell mediated rejection in one patient and viral nephropathy in five patients. Non-specific histological findings were determined in five patients.

Conclusion: Early recognition of the etiology of graft dysfunction that develops at 1 year and appropriate treatment will contribute to the preservation of long-term graft dysfunction.

Keywords: Renal transplantation, children, acute graft dysfunction

Introduction

Kidney transplantation has been the preferred long-term treatment of choice in children with end stage renal disease (ESRD) since 1954 (1). Prognosis and graft survival outcomes among pediatric transplant recipients has improved significantly over the past two decades as a result of improvements in surgical care, immunological management, infection control and improvements in

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Received: *02.09.2020* **Accepted:** *03.12.2020*

cardiovascular care. However, allograft dysfunction (AGD) is the most common complication of renal transplantation and it has complex and critical outcomes for the long-term graft function and graft survival and can lead to graft loss (1,2).

Acute renal AGD has been defined as one or more of the following criteria: an increase in serum creatinine over 25 percent from baseline, failure of serum creatinine to decrease following transplantation and/or proteinuria >1 gr/day (3). Graft dysfunction has been divided into three categories based on the timing of presentation: delayed graft function (DGF) in the first week after transplantation, early graft dysfunction within the first six months after transplantation and late graft dysfunction after six months. The approach to diagnosis and treatment of AGD is determined by this categorization. Post-operative graft dysfunction within the first week, known as DGF, mostly presents with failure in the decrease of serum creatinine and oliguria or anuria (4). In the initial post-transplant hours and days, surgical complications (urine leaks, urinary obstructions), thrombosis of the transplant renal artery or the transplant renal vein and hyperacute rejection tend to occur (4). In addition, expanded criteria donor kidneys have been associated with a higher risk of ischemic injury and DGF in this period (5). In the early period after transplantation, the most common causes of graft dysfunction have been reported to be acute rejection, calcineurin inhibitor nephrotoxicity, thrombotic microangiopathy, recurrence of primary disease, renal artery stenosis in the transplanted kidney, viral infections and *de novo* glomerular diseases (4,5). There are a limited number of studies on early AGD in the literature and also these studies have focused on adults.

In this article, we aimed to present the etiological factors of treatment strategies for, and treatment responses to AGD in the first year after renal transplantation in children.

Materials and Methods

The data of children with AGD in the first year after kidney transplantation between March 2005 and October 2017 were analyzed retrospectively in this study. All patients who had received a kidney transplant at less than 18 years of age were included. "AGD" was defined as an acute increase in creatinine levels by 25% or more compared to the baseline. AGD episodes within first year after transplantation are defined as early ADG. "DGF" was defined as the need for dialysis treatment during the first week after transplantation due to dysfunctional graft. Gender, age at the time of transplantation, the etiology of the chronic kidney disease, pre-transplant dialysis programs and durations, donor characteristics (living or cadaveric), heliotype matches, and the cold ischemia times of those patients diagnosed with AGD were recorded. The patients were evaluated for AGD episodes, time of diagnosis, increases in creatinine levels, and the presence and amount of proteinuria. The main causes of AGD were classified as either "immunological" or "non-immunological". Acute rejection, mediated by T-cells (acute cellular rejection) or antibodies (acute antibody-mediated rejection) were classified as immunological causes; conversely, infections [urinary tract infections (UTIs)], dehydration, calcineurin inhibitors (CNIs) toxicity, viral nephropathy [Cytomegalovirus (CMV), BK virus infections] and urinary obstruction were grouped as non-immunological factors. The number of biopsies for diagnosis and pathological findings were recorded. The treatments initiated according to the diagnoses and the responses to these treatments were evaluated according to decreases in creatinine and proteinuria levels. This retrospective analysis was approved by the local Ethics Committee, İzmir Katip Çelebi Non-Interventional Clinical Studies Institutional Review Board (date: 08/08/2019, no: 315).

Statistical Analysis

Categorical data were described using frequencies and percentages. Continuous data were described using the mean and standard deviation for normally distributed data. The distribution of baseline characteristics across categories of the exposure variable was evaluated using parametric statistics as appropriate. All statistical analyses were performed using SPSS version 18.0.

Results

Over the 12-year period, 55 pediatric renal allograft patients were followed up in our clinic. During this long follow-up period, 25 patients (45%) were diagnosed with early AGD with 30 AGD episodes in total (five patients were admitted twice in the first year). The mean age of the patients was 12.6 (4.0±21.0) years, with a male to female ratio of approximately 2:1. Sixty percent of patients received renal allograft from a living donor and 40% of patients received renal allograft from a deceased donor. All living donors were related donors such as the parents of the patients. The underlying etiologies of ESRD were congenital urologic abnormalities in 14 (56%), chronic pyelonephritis in five (20%), chronic tubulopathy in two (8%), hemolytic uremic syndrome in one (4%), amyloidosis in one (4%) and renal cystic disease in two (8%) cases. Five children (39%) had pre-emptive transplantation, 12 children (61%) had a transplant after a variable duration

of peritoneal dialysis and 8 children had a transplant after a period of hemodialysis. The average duration of the dialysis program was 31.2 months (1-120 months). Five recipients showed one heliotype match, four recipients showed two heliotype matches, seven recipients showed three heliotype matches, eight recipients showed four heliotype matches and only one recipient showed five heliotype matches. The mean cold ischemia time for renal allograft was 7.4 hours (1-24 hours). Zero-time allograft biopsies were mostly reported (21 patients) as normal glomerular morphology. Allograft biopsy materials revealed minimal intimal sclerosis in one patient and acute tubular necrosis in two recipients. The allograft biopsy report of a recipient who had transplantation in another center was missing. DGF occurred in four patients (16%). The allograft functions improved over an average of five days in these recipients (Table I).

Patients had early AGD at an average of 4.2 months (1-10 months) after transplantation. The mean level of increase in creatinine was 0.66 mg/dL (0.3-3.5 mg/dL). Urine analysis revealed non-nephrotic proteinuria in 14 patients and nephrotic proteinuria in three patients at the time of diagnosis. Proteinuria was not observed in 13 patients. The underlying etiologies of early AGD were immunologic in 10% and non-immunologic in 90%. Non-immunologic factors were UTI in five (16.7%), CMV nephropathy in one (3.3%), BK nephropathy in five (16.7%), acute CNI toxicity in eight (26.7%), dehydration in seven (23.3%) and urological anomalies in one patient (3.3%) respectively. Upon the diagnosis of AGD, 12 patients underwent renal allograft biopsy. Histological findings were consistent with T-cell mediated rejection in two patients (8%); B-cell mediated rejection in one patient (4%) and viral nephropathy in five patients (20%). Non-specific histological findings were determined in five patients. In 18 AGD episodes, biopsy was not performed.

For AGD treatment, intravenous hydration was performed in seven patients. Antibiotic treatment was given to six patients with graft dysfunction due to UTI, and antiviral protocols were applied to five patients who were diagnosed with viral nephropathy. CNI dose was regulated in eight patients who had acute CNI toxicity. One patient who had post-renal obstruction in the transplant kidney was surgically treated. Two patients who were diagnosed with acute cellular rejection as the cause of AGD received pulse corticosteroid and one patient with B-cell mediated rejection received pulse corticosteroid and intravenous immunoglobulin. In the follow-up of the patients, mean creatinine level decreased 0.5 mg/dL (-3.0-0.0) by the end of the first week, 0.49 mg/dL (-3.0-0.0) by the end of the second week, 0.48 mg/dL (-2.9-0.4) by the end of the third week and 0.56 mg/dL (-3.40-0.20) by the end of the fourth

Table I. Pretransplant futures of patients with AGD

No of AGD patient/All patient, n (%)	25/56 (44.6)
Gender (female/male), n (%)	8 (32)/17 (68)
Tx age, (year) (min-max, mean ± SD)	4-21, 12.6±4.3
Tx donor (living/chadaveric), n (%)	15 (60)/10 (40)
Etiology of CKD, n (%)	
Urological (CAKUT)	14 (56)
Non-urological	11 (44)
Chronic glomerulonephritis	5 (20)
Chronic tubulopathy	2 (8)
Renal cystic disease	2 (8)
HUS	1 (4)
Amiloidosis	1 (4)
Dialysis types, n (%)	
Preemptive	5 (20)
PD	12 (48)
HD	8 (32)
Duration of dialysis (year) (min-max, mean ± SD)	0.1-10, 2.6±2.2
Residue urine volume (anuria/oliguria/ >500 cc), n (%)	4 (16)/5 (20)/16 (64)
HLA match	
1 match	5
2 match	4
3 match	7
4 match	8
5 match	1
DGD, n (%)	4/25 (16)
Cold ischemia time (hour) (min-max, mean ± SD)	1-24, 7.4±7.9
Urine volume in first hour after Tx (cc) (min-max, mean ± SD)	250-10,100, 4081±2830
Zero-time renal transplant biopsy n (%)	
Normal	21 (84)
Generalized ATN	2 (8)
Mild intimal sclerosis	1 (4)
Missed	1 (4)

AGD: Acute graft dysfunction, DGD: Delayed graft function, Tx: Transplantation, SD: Standard deviation, CKD: Chronic kidney disease, CAKUT: Congenital abnormalities of kidney urinary tract, HUS: Hemolytic uremic syndrome, PD: Peritoneal dialysis, HD: Hemodialysis, ATN: Acute tubular necrosis, min: Minimum, max: Maximum

week. Four weeks after the treatment, mean creatinine levels decreased 0.56 mg/dL. Nephrotic proteinuria was detected in two, and non-nephrotic proteinuria was detected in 12 cases (Table II). Creatinine levels did not decrease to basal level in eight patients. Three of these patients were diagnosed with BK virus nephropathy, three had UTIs, and one patient had B-cell mediated rejection. All patients with AGD secondary to acute dehydration, CNI toxicity, urological and vascular pathologies were detected to have decreased to basal values of creatine levels after treatment.

Table II. Clinical properties of patients with AGD

No of AGD/No of patient with AGD/ All patient, (n)	30/25/56
AGD time after transplantation (month), (min-max, mean ± SD)	1-10, 4.2±2.3
Etiology of AGD, n (%)	
Immunologic	3 (10)
T-cell rejection	2 (6.6)
B-cell rejection	1 (3.4)
Non-immunologic	27 (90)
Infection	18 (60)
AGE-induced dehydratation	7 (23.3)
UTI	5 (16.7)
BKV	5 (16.7)
CMV	1 (3.3)
CNI toxicity	8 (26.7)
Ureterovesical obstruction	1 (3.3)
AGD biopsy findings, n (%)	12/30 (40)
Non-specific	5 (41.7)
Viral nephropathy	4 (33.3)
T-cell rejection	2 (16.7)
B-cell rejection	1 (8.3)
Treatment, n (%)	
CNI dose regulation	8 (26.6)
IV hydration	7 (23.4)
Antibiotic	6 (20)
Antiviral	5 (16.6)
Steroid+IVIG	3 (10)
Graft ureteroneocystostomy	1 (3.4)
Δcreatinine, (mg/dL) (min-max, mean ± SD)	
During AGD	(0.3-2), (0.56±0.38)
After 4 weeks AGD	[(-1.9)-(-0.2)], [(-0.47) ±(-0.49)]
No of patient with proteinuria, (nephrotic/non-nephrotic/ normal) (n)	
During AGD	3/12/10
After 4 weeks AGD	3/12/10

AGD: Acute graft dysfunction, Tx: Transplantation, SD: Standard deviation, AGE: Acute gastroenteritis, UTI: Urinary tract infection, BKV: BK virus CMV: Cytomegalovirus, CNI: Calcineurin inhibitors, min: Minimum, max: Maximum

Discussion

AGD is the most common complication of renal transplantation that can lead to graft loss. It usually manifests as an increase in the serum creatinine concentration with a decrease in the estimated glomerular filtration rate (eGFR) (4). Proteinuria, renal tubular dysfunction and reduction in urine output are the other presentations of AGD (4). There are several causes of early AGD. Some causes tend to occur in the initial post-transplant hours and days whereas others occur in the first few weeks and months after transplantation (4). Hyperacute rejection and thrombosis of the renal artery or vein are serious causes of early AGD that occur in the initial hours after transplantation (6). Neither thrombosis nor hyperacute rejection were detected as a cause of early AGD in any of our patients.

The most frequent cause of AGD is toxicity from CNI that are used in transplantation for their high effectivity in preventing allograft rejection. AGD caused by CNI can occur acutely in a reversible form leading to irreversible structural damage, and it can be attributed to contribution of chronic calcineurin toxicity to long-term renal AGD (7,8). Nephrotoxicity secondary to CNIs has been reported to occur in 76% to 94% of kidney transplant recipients (9). In previous studies, CNI toxicity has been shown in two retrospective case-control studies and 10 cohort studies. CNI toxicity was defined by renal biopsy in five studies, with clinical indexes (eGFR/Scr/FK506 concentration) in four studies and with DGF-designated in three studies. In five studies, patients received cyclosporine treatment while in seven studies they received tacrolimus therapy (10-22). In our study, it was found that 8 of the 30 acute cases of AGD were due to calcineurin toxicity.

Immunosuppressive drugs improve renal graft survival and function, but it has been proven that they contribute significantly to most post-transplantation infectious diseases (23). Gastrointestinal infections are the most common infectious diseases adversely affected by immunosuppression in transplant recipients. The major symptoms are abdominal pain, diarrhea, nausea, vomiting and dyspepsia, which are inconvenient and unpleasant for the patient (24). With infected enterocytes, changes

in immunosuppressive drug metabolism occur and irregular blood drug levels can be seen. These infections are associated with an increased risk of AGD due to dehydration and irregular immunosuppressive drug levels (25,26). In a DIDACT study that defined the etiology and treatment of severe diarrhea in renal graft recipients, 67% of patients were diagnosed with AGD (24). We observed seven renal transplant recipients (23%) with AGD secondary to gastrointestinal infections and hypovolemia in 30 early AGD periods.

The second most frequent infectious complication is UTIs (27). Some studies have evaluated the impact of UTIs on renal allograft function (27-30). Studies evaluating all UTIs concluded that UTIs do not cause AGD (28,29); however, there is still no definitive conclusion. Pelle et al. (30) associated UTIs with impaired renal allograft function measured by eGFR within 4 years of follow-up time in kidney allograft recipients. Singh et al. (27) observed impaired renal allograft function measured by eGFR and 24-hour urine protein excretion during UTIs. The allograft functions were normalized in all patients within one month subsequent to treatment of UTIs. Similar to these studies, in our study, UTI was the etiology of early AGD in 5 patients and graft functions normalized with treatment in all of them.

BK virus is an opportunistic infectious virus, threatening renal function especially during the first year after transplantation (31). The virus remains latent in genitourinary cells after primary infection and can reactivate in immunocompromised kidney transplant recipients usually in the first year. Tubulointerstitial nephritis is frequently seen in the early period of infection while ureteral stenosis may occur in the late period (32). In one research study, the mean rate of graft loss due to BK virus nephropathy was reported to be 46.2% and in another study the rate of allograft loss was reported to be higher than the above-mentioned average (66.7%) (33,34). In our study, BK virus nephropathy was determined in five patients (16.7%). All cases with BK nephropathy were treated by immunosuppressive dose reduction and intravenous immunoglobulin. Mycophenolate mofetil treatment was discontinued and leflunomide treatment was started in 3 patients who could not achieve the expected decrease in BK virus copy levels and continued graft dysfunction. Creatinine levels were reduced to basal levels in only two patients after four weeks of treatment and in other patients, creatinine levels decreased to basal levels after leflunomide treatment during the fourth month. In one patient, the etiology of early acute graft dysfunction was CMV, another opportunistic viral infection. After CMV treatment was applied to this patient, their creatinine value decreased to a basal value.

Acute rejection is one of the causes of early graft dysfunction and can occur due to T-cell mediated cellular rejection or antibody-mediated acute humoral rejection (32). The incidence of acute allograft rejection for first-year post-transplant patients was reported to be 8% by the Organ Procurement and Transplantation Network in 2014 (2). Most acute rejection episodes were reported among the first six months after transplantation and most patients with acute rejection episodes are asymptomatic. Patients usually present with an increase in creatinine level, and rarely with a reduction in urine output, graft pain or tenderness (35). In our study, acute rejection was determined to be 10% in acute graft failures in the first year in accordance with the literature. In the biopsies of cases with acute rejection, T-cell rejection was determined in two cases and B-cell rejection was determined in one case. All cases presented with acute graft failure and there was no clinical symptom in any case.

Another complication of renal transplantation which causes AGD is ureteral or bladder related obstructive uropathy (32,36). Ureteral obstruction can be caused by extrinsic pathologies (compression by urinoma, lymphocele, or hematoma) or intrinsic factors (ureteral edema, blood clots, stones, or strictures). Ureteral stenosis is reported to occur in 2.4% to 6.5% of kidney transplants (37). Most ureteral complications were reported to occur during the first year after renal transplantation (32). In our study, urological pathology causing renal graft failure in first year of transplantation was determined in only one patient. In addition, the cause of the ureteral obstruction was not related to the transplantation surgery. A hematoma formed after surgical procedure for post-transplant vesicoureteral reflux in the post-transplant 6th month causing ureteral stenosis and graft failure.

There are few studies and reports on acute graft dysfunctions and its etiology in the first year after renal transplantation. In the present study of the etiology of early AGD, it can be seen that the ratio of immunological etiologies is lower compared with previous studies (37,38). However, high blood levels of CNI that frequently associated with immunosuppressive drugs and UTIs are seen at a higher rate in AGD etiology in our study. The causes of early graft dysfunction may vary with medical and surgical treatment modalities which can change over time. The determination of the causes of graft dysfunction and its early treatment can lead to improvements in graft survival and prognosis.

Conclusion

In conclusion, non-immunologic causes of early AGD have been observed with the increase in the effectiveness of immunosuppressive therapies. Early recognition and appropriate treatment of AGD etiology can contribute to a rapid recovery of graft function.

Ethics

Ethics Committee Approval: This retrospective analysis was approved by the local Ethics Committee, İzmir Katip Çelebi Non-Interventional Clinical Studies Institutional Review Board (date: 08/08/2019, no: 315).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ö.Y., Design: B.K.D., Data Collection or Processing: E.S., Analysis or Interpretation: S.A.Ç., Literature Search: F.M., Writing: E.S., Ö.Y., D.A., C.A., T.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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J Pediatr Res 2021;8(4):389-93
DOI: 10.4274/jpr.galenos.2020.50251

Original Article

Effects of 12-month Antiepileptic Drug Use on Thyroid Functions in Children: A Retrospective Observational Study

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ABSTRACT

Aim: The purpose of this study was to examine the effects of antiepileptics on thyroid function tests and to compare these effects among different antiepileptics.

Materials and Methods: Two hundred and twenty patients (102 female and 118 male) aged 1-17 years indicated for antiepileptic drug (AED) therapy for epilepsy were enrolled in this study which was performed in a child neurology clinic between January 2014 and January 2018. Those patients using a single AED and with complete seizure control were included. In this study period, according to the local protocol, we measured free thyroxine (fT4) and thyroid-stimulating hormone (TSH) levels at the beginning of treatment and at the 12th month of AED therapy.

Results: The mean age of the patients was 10.2±4.4 years. TSH elevation was observed in only eight patients. These eight patients' thyroid autoantibodies were negative and their thyroid ultrasonography were normal. Subclinical hypothyroidism (TSH: 5-10, fT4 normal) was present in three of these eight patients, and they were therefore not started on medication. The other five were started on L-thyroxine. Four of these were using valproic acid and one was using carbamazepine. We found no significant difference between TSH and fT4 levels measured before the start and at the 12th month of drug therapy, nor among the different AEDs used.

Conclusion: AEDs have no marked effects on thyroid function, and may therefore be safely used from that perspective.

Keywords: Antiepileptic drugs, children, epilepsy, thyroid function

Introduction

Epilepsy is the most common pediatric neurological disorder. Antiepileptic drug (AED) therapy represents the primary therapeutic option, although patients often require long-term and even life-long treatment (1).

Epilepsy and AEDs can target various substrates to affect hormone levels, including the limbic system, hypothalamus, pituitary, peripheral endocrine glands, liver, and adipose tissue (2,3). Recent years have seen growing interest in the impact of epilepsy itself and of AED therapy on alterations in thyroid hormones and metabolism. Different studies evaluating thyroid functions in patients with epilepsy suggest no changes in direct association with epilepsy, although some changes in thyroid function tests may occur

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Received: *20.10.2020* **Accepted:** *10.12.2020*

with the use of some AEDs (3,4). However, other studies have reported that AEDs have no effects on thyroid function tests (5).

Many AEDs are capable of altering thyroid hormone homeostasis in terms of biosynthesis, release, transport, metabolism, and excretion of thyroid hormones. AEDs are strongly associated with decreased T4, free thyroxine (fT4), T3, and rT3 levels (6-8). It has been suggested that the alteration in thyroid parameters observed in patients using AEDs may be attributable to an effect of these drugs on binding proteins the stimulation of hepatic degradation or conjugation of thyroid hormones or a modification of peripheral deiodinase activity (9-11).

The purpose of this study was to examine the effects of antiepileptics on thyroid function tests (fT4 and TSH), and to compare these effects among different antiepileptics.

Materials and Methods

This research was designed as a retrospective hospital-based cohort study. Two hundred and twenty patients aged 1-17 years and denoted for AED treatment for epilepsy were admitted and followed up by a single physician in a child neurology clinic between January 2014 and January 2018. Epilepsy was diagnosed based on the ILAE-2017 diagnostic and clinical criteria (12). The inclusion criteria were as follows; aged 1-17 years at diagnosis, the receipt of monotherapy with valproic acid (VPA) or another AED with follow-up for at least one year, complete control of seizures for 12 months, the absence of systemic or central nervous diseases (other than epilepsy) capable of interfering with hypothalamic-pituitary-gonadal or thyroid functions, normal findings at brain magnetic resonance imaging, and no previous treatment with AEDs, contraceptives, or hormonal or psychotropic medications. Written informed consent to participate was obtained from all families. In this study period, according to the local protocol, we measured fT4 and thyroid-stimulating hormone (TSH) levels at the beginning of treatment and at the 12th month of AED therapy. Mean daily dosages were 30 mg/kg/day for VPA, 5 mg/kg/day for phenobarbital (PB), 30 mg/kg/day for carbamazepine (CBZ), 30 mg/kg/day for oxcarbazepine (OXC), 40 mg/kg/day for levetiracetam (LEV), 5 mg/kg/day for lamotrigine (LMT), and 5 mg/kg/day for topiramate (TPM). Patients with structural brain lesions, neuro-metabolic disease, thyroid diseases (hypothyroidism, hyperthyroidism etc.) severe mental retardation, antiseizure drug resistant seizures, or needing multi-antiseizure drug therapy were excluded. Also, those patients who missed the 12th month check-up were excluded from the study. All electroencephalography findings of the patients were evaluated by the same child neurologist and they were classified as either mild, moderate or severe.

Patient group serum blood analyses were performed in our hospital's biochemistry laboratory. Blood samples were obtained between 08.00 a.m. and 10.00 a.m. after overnight fasting. Five cubic centiliter specimens were placed into gel-containing tubes. Care was taken to ensure that the tourniquet was applied for less than 1 minute during blood collection. Blood placed into gel-containing tubes was allowed to clot for 20 minutes at room temperature to prevent hemolysis during centrifugation. Sera were separated by centrifugation for 15 minutes at 3,000 rpm, and analysis was performed within 2 hours. Thyroid hormones and TSH were analyzed using the ECLIA method on a Boehringer Manhaim E170 device. Normal thyroid hormone levels according to that method are free T4 (fT4)=0.93-1.7 ng/mL and TSH=0.27-4.2 uIU/mL, and normal thyroid autoantibody levels are anti-thyroperoxidase=0-34 IU/mL and anti-TG=0-115 IU/mL. Ethical approval for the study was granted by the Bolu Abant İzzet Baysal University Clinical Researches Ethical Committee (2020/136).

Statistical Analysis

Continuous data were expressed as mean ± SD (minimum-maximum), and categorical variables as frequency and percentage values for each group. The Kolmogorov-Smirnov test was first applied to determine the normality of distribution of the variables. The dependent samples t-test was applied to normally distributed variables, while Pearson's chi-square test and Fisher's exact test were applied to categorical variables. The results were assessed within 95% reliance and at a significance level of $p<0.05$. Analyses were performed on Statistical Package for Social Sciences 25.0 for Windows software (SPSS Inc., Chicago, Illinois, USA).

Results

The mean age of the 220 patients (102 female, 118 male) included in this study was 10.2±4.4 years. Ninety-seven patients were using VPA, twenty-six were using CBZ, thirty-four were using OXC, twenty-seven were using LEV, seven were using LMT, nine were using TPM, and twenty were using PB. Mean fT4 was 1.12±0.27 (0.7-2.26) at month 0 and 1.09±0.28 (0.6-2.23) at month 12, while mean TSH was 2.56±1.3 (0.62-9.97) at month 0 and 2.82±2.02 (0.64-14.1) at 12 months (Table I). TSH elevation was detected in only eight patients during follow-up. These eight patients' thyroid autoantibodies were negative and their thyroid ultrasonography were normal. Subclinical hypothyroidism was present in three of these eight (TSH<10, fT4 normal),

Table I. Characteristics of the epilepsy patients

Variables	n (%) or mean ± SD (range)
Age	10.27±4.4 (1-17)
Gender	
Female	102 (46.4)
Male	118 (53.6)
fT4 (month 0)	1.12±0.27 (0.7-2.26)
fT4 (month 12)	1.09±0.28 (0.6-2.23)
TSH (month 0)	2.56±1.3 (0.62-9.97)
TSH (month 12)	2.82±2.02 (0.64-14.1)
AED	
VPA	97 (44.1)
CBZ	26 (11.8)
OXC	34 (15.5)
LEV	27 (12.3)
LMT	7 (3.2)
TPM	9 (4.1)
PB	20 (9.1)
Anti Tg/Tpo	
No	212 (96.4)
Negative	8 (3.6)
Thyroid USG	
No	212 (96.4)
Thyroiditis	8 (3.6)
L-tiroksin	
No	215 (97.7)
Yes	5 (2.3)

Data expressed as n (%)
SD: Standard deviation, Ft4: Free thyroxine, TSH: Thyroid-stimulating hormone, AED: Antiepileptic drug, VPA: Valproic acid, PB: Phenobarbital, CBZ: Carbamazepine, OXC: Oxcarbazepine, LEV: Levetiracetam, LMT: Lamotrigine, TPM: Topiramate, USG: Ultrasonography

and these were therefore not started on medication. The remaining five patients were started on L-thyroxine. Four of the five were using VA and one was using CBZ.

The effects of the AEDs on fT4 serum levels are shown in Table II. No statistically significant difference was determined between fT4 serum levels and the different AEDs used before the start of treatment and after 12 months of drug therapy.

The effects of the AEDs on TSH serum levels are shown in Table III. No statistically significant difference was determined between TSH serum levels and AEDs investigated before the start of treatment and after 12 months of drug therapy.

Table II. Effects of AEDs on fT4

Variables	fT4 (initial)	fT4 (12 month)	p-value
AEDs			
VPA	1.11±0.23	2.13±9.7	0.3[a]
CBZ	1.11±0.34	1.0±0.18	0.1[a]
OXC	3.74±1.5	1.07±0.35	0.32[a]
LEV	1.07±0.16	1.03±0.24	0.39[a]
LMT	1.2±0.27	1.04±0.24	0.28[a]
TPM	1.08±0.37	0.9±0.15	0.1[a]
PB	1.28±0.38	1.2±0.27	0.33[a]

[a]Paired sample t-test
AED: Antiepileptic drug, Ft4: Free thyroxine, VPA: Valproic acid, CBZ: Carbamazepine, OXC: Oxcarbazepine, LEV: Levetiracetam, LMT: Lamotrigine, TPM: Topiramate, PB: Phenobarbital

Table III. Effects of AEDs on TSH

Variables	TSH (initial)	TSH (12 month)	p-value
AEDs			
VPA	2.82±1.51	3.07±2.28	0.22[a]
CBZ	2.26±1.05	2.69±2.0	0.26[a]
OXC	2.3±1.19	2.41±1.39	0.64[a]
LEV	2.1±0.85	2.34±1.5	0.44[a]
LMT	2.54±0.84	3.1±2.4	0.1[a]
TPM	3.07±1.42	2.76±1.8	0.6[a]
PB	2.46±0.9	3.02±2.24	0.29[a]

[a]Paired sample t-test
TSH: Thyroid-stimulating hormone, AED: Antiepileptic drug, VPA: Valproic acid, CBZ: Carbamazepine, OXC: Oxcarbazepine, LEV: Levetiracetam, LMT: Lamotrigine, TPM: Topiramate, PB: Phenobarbital

Discussion

This study determined no statistically significant effects on thyroid functions for drugs such as VPA, CBZ, OXC, LEV, FB, TPM, and LMT used as single antiepileptics. Also, no significant differences between these medications in terms of thyroid function tests were determined. TSH elevation was detected in eight patients (3.6%) at the end of a 12-month follow-up of thyroid dysfunction. Subclinical hypothyroidism was detected in three of these, who were therefore not started on medication. Five patients were started on L-thyroxine due to TSH elevation and low fT4. Four of these patients were using VPA and one was using CBZ. Some studies have reported that antiepileptics, and particularly VPA, have adverse effects on thyroid function tests (13,14), while others have reported no effect (5).

One study comparing 41 epileptic patients using VPA with a control group reported significant elevation in fT4 and

TSH levels, particularly in the first four years of treatment, in approximately one in three patients using VPA (13). A similar study compared 61 epileptic children using VPA with a 144-member healthy control group and reported a higher incidence of subclinical hypothyroidism in the VPA group (14). Based on these findings, those authors suggested that subclinical hypothyroidism may frequently emerge during VPA use. Although the follow-up period was shorter in the present study, we detected hypothyroidism in only four patients using VPA, and subclinical hypothyroidism in three patients. Caksen et al. (5) compared thyroid and parathyroid functions in 31 patients with epilepsy using VPA with an aged-matched control group and reported no effect of long-term VPA therapy on thyroid and parathyroid functions in children. In addition, they concluded that VPA can be safely used in children from that perspective without causing thyroid or parathyroid dysfunction.

Another study in which 42 girls used VPA and 15 used other AEDs reported higher TSH levels at six and 12 months in the VPA group with thyroid function tests performed at months 0, 6, and 12, while no significant difference was observed between VPA and other AEDs in terms of mean fT4 levels (15). In the present study, we determined no significant difference between fT4 or TSH levels at months 0 and 12.

In another study involving 183 pediatric epilepsy patients using VPA or PB and 151 healthy controls, subclinical hypothyroidism was detected at month 12 in 15.2% of the VPA group and in 2.9% of the PB group. A statistically significant difference was observed in the incidence of subclinical hypothyroidism in the VPA group compared with pre-treatment values, while no significant difference was found in the PB group (16). The rate of development of hypothyroidism in the VPA group in the present study was 4.1% (4/97), and no significant difference was determined compared to other AEDs.

A prospective study of 21 epileptic patients using LEV or CBZ investigated thyroid function tests and lipid profile values before the commencement and one and six months after the commencement of medication. The authors reported a significant decrease in fT4 levels in the CBZ group but no significant change in fT4 or TSH levels in the LEV group (17). TSH elevation and low fT4 were determined in only one patient receiving CBZ in the present study. We observed no significant change in fT4 or TSH levels in those patients using LEV. There was also no difference between the two drugs from that perspective.

A study of 223 patients with controlled epilepsy using single AEDs investigated fT4 and TSH levels at months 0, 6, and 12. Lower serum fT4 levels and increased serum TSH levels were reported in those patients treated with VPA compared to those using CBZ, OXC, or FB. No difference in thyroid function tests was observed in patients using (18). In the present study, TSH elevation and low fT4 were detected in four patients using VPA and one using CBZ, while no difference in thyroid functions tests was found in any of the other AEDs.

A study involving 78 girls receiving CBZ, OXC, or VPA monotherapy and a 54-member healthy control group reported low fT4 and normal TSH in the CBZ and OXC groups, compared to normal fT4 and high TSH in the VPA group (19). We detected no difference between mean fT4 and TSH in the present study.

Garoufi et al. (20) investigated 23 children aged 5-15 years using OXC and measured fT4 and TSH levels before the start of drug therapy and after 8 and 18 months. fT4 was significantly decreased at 8 and 18 months ($p<0.001$ and $p=0.002$, respectively), while TSH levels were significantly increased at 8 and 18 months. In the present study, there was no difference between either fT4 or TSH levels at months 1 and 12.

Consistent with the results of the present research, another study of 53 patients aged 3-17 years using VPA, CBZ or OXC monotherapy also observed no difference in thyroid function tests and thyroid volumes between the study groups. The authors of that study detected hypothyroidism based on the thyrotropin-releasing hormone stimulation test in six patients using VPA, in one using CBZ, and in one using OXC (21).

In a study of 106 patients aged from 3 months to 14 years using VPA, CBZ, OXC, LEV, TPM, or PB monotherapy, fT4 and TSH levels were measured at the start of treatment and at months 3, 6, and 9. No significant differences were observed in mean fT4 values between the drug groups. However, the mean fT4 levels of the patients in the VPA group exhibited a decrease within the observation period. No significant difference was observed in mean TSH values between the groups at the beginning and at the third and sixth months. However, by the 9th month, TSH values had increased significantly in the VPA group. In the VPA group, mean TSH values rose progressively but remained within normal limits. Thyroid dysfunction was detected in 21 patients during follow-up (19.6%). The authors of that study suggested that VPA use might lead to thyroid dysfunction in epileptic patients (22).

Study Limitations

The limitations of the present study include its retrospective nature, the lack of a healthy control group, the follow-up period being restricted to 12 months, and thyroid function tests not being investigated between months 0 and 12. However, the particular strengths of the study include the high patient number and that the hitherto unexamined relationship between AEDs and thyroid function tests was investigated.

Conclusion

In conclusion, AEDs have no marked effect in terms of thyroid functions, and may therefore be used safely from that perspective. However, further prospective studies involving larger patient numbers and followed up for longer periods are needed with regard to this subject.

Ethics

Ethics Committee Approval: Ethical approval for the study was granted by the Bolu Abant İzzet Baysal University Clinical Researches Ethical Committee (2020/136).

Informed Consent: Written informed consent to participate was obtained from all families.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: F.H., K.A.B., Design: F.H., K.A.B., N.K., Data Collection or Processing: A.T., Analysis or Interpretation: M.D., Literature Search: S.T., Writing: N.K.

Conflict of Interest: None of the authors had conflict of interest.

Financial Disclosure: The authors declared that this study received no financial support.

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J Pediatr Res 2021;8(4):394-400
DOI: 10.4274/jpr.galenos.2020.46354

Original Article

Children's Coronavirus Agenda: Qualitative Study

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ABSTRACT

Aim: Public health emergencies are not easy for anyone to comprehend or accept and many young children can feel frightened and confused in this process. This study was carried out to determine how the coronavirus disease-2019 experiences of children were evaluated by their parents.

Materials and Methods: A qualitative research method was used in this research. The data were collected using a socio-demographic data form and a semi-structured questionnaire. The data of the research were obtained via online methods due to the continuing social isolation measures in Turkey. The study was completed with 28 parents. The data obtained were analysed by thematic coding.

Results: Three main themes have been identified regarding the coronavirus agenda of children: (1) children's questions about coronavirus, (2) children's statements about coronavirus, (3) children's reaction to the process. Two sub-themes were identified in each theme. It was found that the children had expressions and questions about corona virus itself, the ways of protection against it, the effects of the virus, what it was and who it would harm. In addition, it was determined that children had emotional and behavioural reactions in this process.

Conclusion: In our study results, it was found that the expressions, questions and reactions of children about coronavirus differ according to their ages. Creating an open environment where children are free to ask questions can help them cope with stressful events and experiences and reduce the risk of permanent emotional problems.

Keywords: Coronavirus, child behaviour, outbreak, qualitative study

Introduction

Coronavirus disease-2019 (COVID-19), which first appeared in people working in an animal market in China in December 2019, has spread to many countries in a short time and has become a global health threat for the whole world (1-3). Due to the rapid spread of the disease and its potentially fatal consequences, emergency action plans have been created in all countries of the world and efforts have been made to reduce the effects of the virus. In Turkey as well, education in schools was suspended for a while and measures were taken to reduce social contact within the scope of the fight against the virus. Both country-wide and family-based measures have led to changes in children's routines.

Although COVID-19 does not pose a serious risk in children, applications such as isolation and restrictive measures, which are confusing for children, can be frightening for them (4). Children may have problems perceiving what is going on around them in this process. Almost all television channels talk about the effects of corona virus, the number of cases, the mortality rates, and the "at risk" groups. Children are often exposed to these conversations on television, social media and via adult speech (5). Children may have difficulties or misunderstand

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Received: *12.08.2020* **Accepted:** *28.12.2020*

the meaning of concepts such as death and illness that are constantly talked about due to their inadequate cognitive perception. One study showed that even children under 2 years of age are aware of the changes around them (6). Their parents' anxiety during this process can cause stress and anxiety in children even if they are not old enough to comprehend the pandemic (7).

This type of situation causes anxiety in children to increase due to factors such as changes of routines and social lives of children. Even if children have heard from the television or adults that the disease is not dangerous for them, they can worry about their elderly relatives who are emphasized to be at risk. Children can express this anxiety in various ways. Children show this by asking their parents various questions, expressing concerns about this situation in their speech, or by changing their behaviour. One study reported that children isolated or quarantined during pandemic diseases are more likely to develop acute stress disorder, adjustment disorder and grief (8). In order to reduce the level of psychological exposure of children, it is very important to answer the child's questions in accordance with their perception level, to listen to their concerns and to provide them with extra love and care (6).

Materials and Methods

The purpose of this study was to discover how COVID-19 is perceived by children, and how they express their concerns with their questions, expressions, emotions and behaviour. For the purpose of this study, in-depth interviews were made with parents.

Recruitment and Eligibility

A qualitative research method was used in this research. With this method, the aim was to investigate how children perceive the situation in depth in order to describe and understand their experiences in detail. The data were collected using a semi-structured questionnaire and the results were analysed thematically. The parents' inclusion criteria are as follows: having children between the ages of 3-18 years old, the absence of diseases that affect the child's cognitive development and also volunteering to participate in the study. The final sample included 28 parents. The sample size was determined to be sufficient for data saturation based on initial reviews of the data and data saturation standards. Data saturation occurs when the themes repeat and no new additional themes arise despite additional data.

Study Procedures

Data Collection

The data of the research were collected via online methods due to the continuing social isolation measures in our country. The participants were told about the purpose and content of the study. The questionnaire consists of two parts, a socio-demographic data form and a semi-structured questionnaire. First of all, the parents filled in the descriptive data form that includes their and their child's socio-demographic characteristics such as age and education level. A semi-structured interview form was used for in-depth, one-on-one interviews. Following this, a semi-structured interview prepared by the researchers was used to determine the children's perceptions, behaviours or concerns about the COVID-19. This form consists of 5 questions. Participants were given the necessary time to express their feelings and thoughts in depth. Interviews were made with the permission of the participants. Each interview lasted approximately 30-35 minutes. The first interview was conducted as a pilot interview, and after this interview, the interview questions were reviewed and those questions that the participants had difficulty in understanding were either rewritten or removed from the form.

Semi-structured interview question

1. Could you tell us what your child is asking you about coronavirus?

2. Could you tell us what your child tells you about coronavirus?

3. Could you tell us what kind of statements your child has made about coronavirus?

4. Could you talk about how your child reacts emotionally to this process?

5. Could you tell us what kind of change you have noticed in your child's behaviour during this process?

Before the study was conducted, ethical permission was obtained from the Ethical Commission of Yozgat Bozok University (protocol number: 95799348-050.01.04-E.9944). The parents were also informed about this study and consent was obtained from the parents before participating in the study.

Statistical Analysis

The IBM SPSS Statistics 22.0 (IBM Corp, Armonk, New York) package software was used to evaluate the data. Socio-demographic data are presented as number and percentage. Qualitative data were analysed using the

content analysis method. The data obtained were analysed by thematic coding. After the expressions were converted into written text, they were examined separately by two researchers and codes corresponding to the discourses were created. The codes obtained were grouped under similar titles and themes were established and the codes were matched with these themes.

Results

The study was completed with 28 parents. Nineteen (67.9%) of the parents were mothers and 9 (32.1%) were fathers. The average age of the fathers was 38 years ±4,846, and the average age of mothers was 35.18 years ±4,675. 28.6% of the mothers and 17.9% of the fathers had only graduated from primary school. 39.3% of the parents had 2 children. The children of the parents interviewed had an average age of 7.36 years and 60.7 % were male. In addition, 60.7% of the children attended school and all of the children who attended school received education regarding coronavirus (Table I).

Three main themes have been identified regarding the coronavirus agenda of children: (1) the children's questions about coronavirus, (2) the children's statements about coronavirus, (3) the children's reaction to coronavirus. Two sub-categories were identified for each theme (Figure 1).

Theme 1. Children's questions about coronavirus

The participants stated that their children asked various questions about the virus and its effects. These questions were analysed and divided into two categories as follows: the effects of the virus and means of protection against the virus.

Sub-theme 1: Questions about the effects of the virus

It was determined that the questions of the children differed according to their ages. Preschool children asked more about the tangible property of the virus. Some parents' statements were as follows:

Parent (P) 21 (Mother: 29 years old/Child: 4-year-old male) "Is our time here? What time is it my son? Isn't it time to die from the corona virus? Why are you saying this? I heard it on TV".

P7 (Mother: 35 years old/child: 4-year-old female) "What does the virus mean? Does the virus have feet?"

It was determined that school-age children are partially aware of disease and its symptoms, and they have questions about staying away from school or getting sick. Some parents' statements were as follows:

Table I. Parents and children descriptive characteristics

Features (N=28)	**Number**	**%**
Father age	38.00±4.846	
Between 25-35 years	9	32.1
36 years old and above	19	67.9
Mother age	35.18±4.675	
Between 25-35 years old	14	50.0
36 years old and above	14	50.0
Mother's educational level		
Primary education	8	28.6
High school	5	17.8
License and above	15	53.6
Father's educational level		
Primary education	5	17.8
High school	6	21.4
License and above	17	60.7
Mother work		
Working	14	50.0
Not working	14	50.0
Father profession		
Officer	15	53.5
Employee	9	32.1
Self-employment	4	14.4
Number of children		
1	10	36.7
2	11	39.3
3 and high	7	25.0
Child's age	7.36±3.402	
3-6 years old	13	46.4
7-12 years old	12	42.9
13 and high	3	10.7
Gender of the child		
Female	11	39.3
Male	17	60.7
School attendance status		
Yes	17	60.7
No	11	39.3
Coronavirus education status		
Yes	17	60.7
No	11	39.3

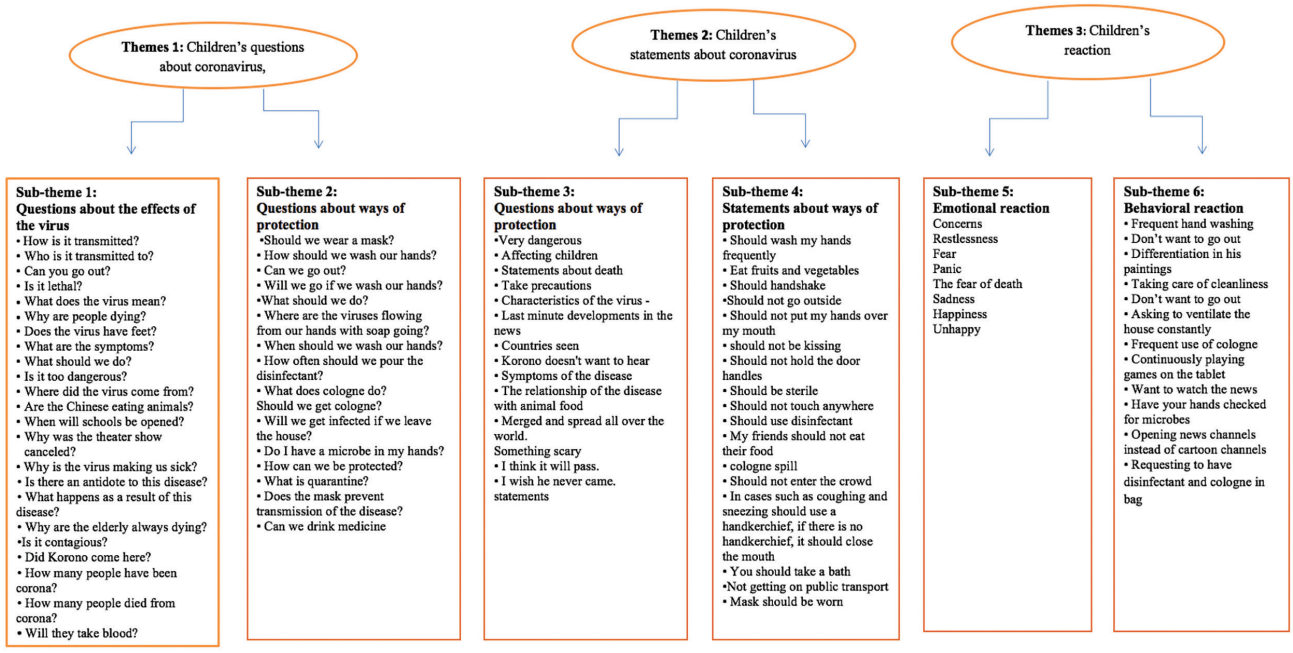

Figure 1. Themes and Sub-theme

P17 (Mother: 32 years old/child: 8-years-old male) "My nose is running. Have I caught coronavirus? Are we not going to school anymore? Does everyone infected die?"

P26 (Mother: 26 years old/child: 8-year-old male) "Did the virus come from China? Did they always eat animals? Is it contagious? Why are old people always dying?"

It was determined that adolescents evaluate the situation mostly with objective data. One parents' statements were as follows:

P10 (Mother: 43 years old/child: 14-year-old male) "How many people have caught corona? How many people have died from corona?"

Sub-theme 2: Questions about ways of protection

Parents stated that their children asked questions about ways to protect themselves against the virus. They asked parents about what kind of measures to take for virus protection. The statements of some parents on this subject were as follows:

P2 (Father: 34 years old/child: 8-year-old male) "Should we wear a mask? How should I wash my hands? Shouldn't I go out?"

P8 (Mother: 38 years/child: 9-year-old female) "When should I wash my hands? How often should I use disinfectant?"

The questions of children in the pre-school period were more concrete expressions.

P7 (Mother: 38 years old/child: 4-year-old female) "Where are the viruses going from our hands with soap? Why do viruses make us sick?"

Theme 2. Children's statements about coronavirus

Children's statements about coronavirus were divided into two categories.

Sub-theme 3: Questions about ways of protection

Some of the statements of the parents were as follows:

P6 (Father: 38 years old/child: 9-year-old female) "It doesn't affect children. It affects the elderly".

P8 (Mother: 38 years old/child: 9-year-old female) "There was a virus and it was transmitted to everyone".

P28 (Mother: 32 years old/child: 7-year-old male) "It appeared because they ate animals in China. It spread all over the world. It is horrible. I think it will pass, but I wish it had never come".

The statements of parents with children of a pre-school age stated that their children think of the virus as a visible, nurtured, human-like creature. Some statements of the participants were as follows:

P7 (Mother: 35 years old/child: 4-year-old female) "I saw it on TV, the feet of the virus were colourful".

P21 (Mother: 29 years old/child: 4-year-old male) "The virus was traveling outside. He was eating. He was sleeping and waking up".

P4 (Father: 37 years old/child: 3-year-old female) "The disease hurts our throat. It leaves you sleepless".

Sub-theme 4: Statements about ways of protection

The participants stated that their children often had expressions about what should be done to protect themselves against the virus.

Some of the parents' statements were as follows:

P1 (Mother: 31 years/child: 4-year-old female) "I have to wash my hands frequently. I should eat plenty of fruit and vegetables. I shouldn't go out too much".

P20 (Mother: 45 years old/child: 7-year-old female) "I should wash my hands frequently, cover my mouth with a handkerchief when sneezing, clover my mouth with the inside of my arm if there is no handkerchief".

P18 (Father: 40 years old/child: 8-year-old male) "We should not enter crowds and touch the places where everyone touches and we should wash our hands".

P25 (Mother: 36 years old/child: 9-year-old male) "Mother, put disinfectant cologne in my bag and put it in front of me at home".

Theme 3. Children's reaction

Parents stated that they observed some emotional and behavioural changes in their children during this process. This theme is divided into two categories based on the statements of the parents.

Sub-theme 5: Emotional reaction

The participants stated that their children were emotionally affected. The emotional responses of the children differed according to their developmental periods.

One parent with a pre-schooler stated that she was happy that her child was at home with her two parents. The parent's statement was as follows:

P12 (Mother: 31 years old/child 4-year-old male) "He is not happy going to nursery because of the holiday and is happy to spend time with both parents at home."

Parents who had a child attending school stated that their children had feelings of anxiety and fear and that they were sad because they were separated from their school and friends.

P8 (Mother: 38 years old/child: 9-year-old female) "I'm so scared. Mother, will we die too?"

P14 (Mother: 39 years old/child: 7-year-old male) "I am very sorry. If the virus gets in you, won't you kiss me?"

P25 (Mother: 36 years old/child: 9-year-old male) "Unhappy for falling behind in social activities".

P17 (Mother: 32 years old/child: 8-year-old male) "He experiences panic due to not going out".

P28 (Mother: 32 years old/child: 7-year-old male) "He feels sad. He is sad that his shows at school were cancelled. He thinks their effort was wasted".

P15 (Mother: 36 years old/child: 9-year-old male) "I know that nothing will happen to me, but I am afraid that my grandparents will be sick".

Sub-theme 6: Behavioural reaction

The parents stated that they observed some behavioural reactions in their children during this process. The statements of the parents regarding this were as follows:

P7 (Mother: 38 years old/child: 4-year-old female) "She wants to go out. She often washes her hands".

P14 (Mother: 39 years old/child: 7-year-old male) "He constantly washes his hands. He wants to ventilate the house constantly".

P17 (Mother: 32 years old/child: 8-year-old male) "He is introverted. He spending his time with the boredom tablet. He communicates very little".

P9 (Father: 39-year-old/child: 4-year-old male) "His paintings have changed. We cannot make sense of them".

Some parents stated that their children watch news programs frequently, although they had never watched them before.

P24 (Father: 41 years old/child: 18-year-old male) "Normally, he doesn't like watching the news. But now, he is constantly watching the news. He tells me in which countries the virus is seen. He describes how it spread, how many people have died".

P2 (Father: 34 years old/child: 8-year-old male) "He does not go out. He wants to wash his hands constantly. He wants to watch the news instead of cartoons".

Discussion

This study examines how the COVID-19 outbreak is perceived by children. The fight against this pandemic has caused children to experience changes in their routines, as is the case in the rest of the society. In our country, curfews have been imposed for people under the age of 20 years old. Factors such as closing schools, being kept away from social environments, or changing play activities can create stress and anxiety in children (9). During this period, most of the media and social conversations are about the epidemic. Children are exposed to the coronavirus speech of the adults around them (6). In our study, it was found that children had expressions about the methods

of protection against coronavirus, the effects of the virus, what it was, who it will harm and how they should be protected. It was also seen that children ask their parents various questions in order to understand the disease and its effects. In addition, it was determined that children respond emotionally and behaviourally. In this study, parents stated that their children had emotional symptoms such as fear, unhappiness, anxiety, and loneliness. In one study conducted in Spain and Italy, their study results appear similar to our results. According to their study, 85.7% of the parents perceived changes in their child's emotional state and behaviour during quarantine, such as increased boredom, irritability, restlessness, nervousness, feelings of loneliness and worries (10).

Cognitive development of children reaches maturity during adolescence (11). In our study, it was found that the questions, speech, behavioural responses and emotional responses of the children differed according to their ages. Especially for pre-school children, what is happening and is spoken about in this process may create confusion and the reason for the measures taken may not be fully understood. In our study, one question from a child was "If nothing happens to children, why are we not leaving home?". Uncertainty increases children's anxiety and stress. Children need honest information about changes in their families and their arrangements. In the absence of this information, children try to understand the situation themselves (12). Children between the ages of 3-6 years look at events in a more concrete manner and have magical and animistic thoughts. The idea that the disease or the condition that he or she is in is a punishment for his or her behaviour may prevail. In our study, pre-school children stated that the virus eats, travels and sleeps, and they have questions about what happens to the virus when they wash their hands. It is important to listen to what children believe and know about COVID-19 so that they do not develop wrong ideas during this period; providing children with an accurate explanation will ensure that they will not be unnecessarily afraid or feel guilty (6). In addition, there should not be much talk about this issue and news should not be watched when children are present.

On the other hand, school children can understand concepts such as microorganisms that may be the cause of the disease, the symptoms of the disease and methods of protection against diseases. Also, in this period, friends, school, teachers and activities are very important for children (11). In our study, it was found that school-age children were upset about cancelled activities at school. It was noted that the children asked their parents questions such as how the virus is transmitted and where it came from. School-age children may be concerned that they or their elders may get sick. This is highlighted by the following statements from a parent with a school age child: "I have a runny nose. Have I become infected with a coronavirus? Are they not going to accept me to school anymore? Does everyone who is infected die?". When we evaluated these statements, it can be seen that the child seems to be worried about getting sick, that this will prevent him or her from going to school and that the child has a fear of death. Another child's statement, "I know that nothing will happen to me, but I am afraid that my grandparents will get sick" shows that he or she is worried about his or her elders. Autonomy is important for children of this age. When our study results were analysed, it was seen that school-age children ask questions about individual measures and exhibit behaviour such as hand washing and airing the room more frequently. It should be explained that children should rest, explanations should be made with simple sentences so that they can understand, and that they are safe when the rules are followed. In addition, giving practical advice that they can apply in their daily lives is important in making children feel that they have the power to control the situation while reducing their risk of infection. In our study, it was stated that the children in the school period watch the news. Watching constant updates about COVID-19 can increase fear and anxiety. Developmentally inappropriate information or information designed for adults can cause anxiety or confusion, especially in young children (13).

The adolescent period is a period when abstract thinking develops and what is happening around them is evaluated realistically. The concept of death is perceived in a similar way to adults (12). For young people who learn from friends and are less dependent on their parents, the situation may differ from young children. Young people tend to trust their friends and the media rather than their families when following an agenda. In our study, parents stated that their children follow the news in this process, although they had never watched it before. More in-depth discussions can be made with children of this age. It is important to direct young people who are exposed to a lot of content from social media to the right resources. Honest, accurate and factual information about the current state of COVID-19 should be provided. It is suggested that adolescents be included in family plans and decision-making processes regarding help with household chores (14). This can also contribute to reducing the exposure of adolescents to social media and digital screens.

Study Limitations

The data of the research were obtained via online methods due to the continuing social isolation measures in our country and the expressions of the parents were used because the children could not be reached directly.

Conclusion

In our study, it was found that the expressions, questions and reactions of children about coronavirus differ according to their ages. Creating an open environment where children are free to ask questions can help them cope with stressful events and experiences and reduce the risk of permanent emotional problems. Accordingly, consideration should be given to the child's age when explaining coronavirus, the changes in daily life due to the virus, and the measures taken against the virus.

Ethics

Ethics Committee Approval: Before the study was conducted, ethical permission was obtained from the Ethical Commission the Yozgat Bozok University (protocol number: 95799348-050.01.04-E.9944).

Informed Consent: Parents were informed about this study and consent was obtained from the parents before participating in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: D.Y.G., R.Y., Design: D.Y.G., R.Y., Data Collection or Processing: S.Ç., D.Y.G., R.Y., Analysis or Interpretation: S.Ç., Literature Search: S.Ç., Writing: S.Ç., D.Y.G., R.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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J Pediatr Res 2021;8(4):401-7
DOI: 10.4274/jpr.galenos.2021.65707

Original Article

The Role of Late Dimercaptosuccinic Acid (DMSA) Scan and Renal Ultrasonography for Vesicoureteral Reflux in Older Children

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ABSTRACT

Aim: Vesicoureteral reflux (VUR) is an important risk factor for urinary tract infection (UTI). We aimed to investigate the relationships between VUR and ultrasound with late dimercaptosuccinic acid (DMSA) scan findings in children aged older than two years who had their first febrile UTI (FUTI).

Materials and Methods: Data from those patients with their first FUTI were retrospectively analyzed. A late DMSA scan was performed at least 6 months after an acute FUTI. The late DMSA scans were graded as mild (focal defect in uptake), moderate (uptake of renal radionuclide from 20 to 40%), and severe (shrunken kidney with uptake less than 20%). Micturating cystourethrography was performed at 3 to 6 weeks after the FUTI.

Results: The records of 220 patients (61 mild VUR, 60 severe VUR, 99 without VUR) were reviewed. An abnormal US was more common in those patients with VUR than those without VUR (p=0.009). Abnormal US had a sensitivity of 79.34% for VUR and 81.67% for severe VUR. The negative predictive value of renal US for severe VUR was 91.13%. The frequency of renal scarring was higher in those patients with VUR than for those without VUR (102/44, p=0.001). A logistic regression analysis showed significant associations between abnormal US and VUR or severe VUR (p=0.019 and p=0.011, respectively). Renal scarring had a sensitivity of 84.3% for VUR, and 91.67% for severe VUR.

Conclusion: Late DMSA scan findings can predict the presence and grade of VUR in older children who have their first FUTI. Normal renal US can predict the absence of severe VUR.

Keywords: Febrile urinary tract infection, late DMSA scan, older children, vesicoureteral reflux

Introduction

Urinary tract infections (UTI) are among the most common infections in childhood (1). The most common abnormality in children with UTI is vesicoureteral reflux (VUR). Children with VUR are at an increased risk of chronic kidney disease; therefore, it is important to determine the presence and grade of VUR in children with febrile UTI (FUTI) (2).

Diagnostic radiological studies in children with FUTI are controversial. The National Institute for Clinical Excellence guideline does not recommend micturating cystourethrography (MCUG) after a child's first UTI (3). In recent years, the emphasis has been on identifying

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Received: *25.10.2020* **Accepted:** *28.01.2021*

patients who are at risk of recurrence of UTI and permanent renal damage rather than detecting VUR. This "top-down" approach implies that VUR has clinical significance only if it causes renal damage. A technetium 99 m-labeled dimercaptosuccinic acid (DMSA) scan is recommended to evaluate permanent renal damage (4).

In this study, we aimed to investigate the relationship between the presence of VUR and renal ultrasonography (US) with late DMSA scan findings in children older than two years who had their first FUTI.

Materials and Methods

The protocol for the present study was reviewed and approved by the Institutional Review Board of Eskişehir Osmangazi University Faculty of Medicine (approval number: 25403353-050.99-E.110593). In this retrospective study, the data of those patients with a first diagnosis of FUTI who were followed up in our Pediatric Nephrology Clinic between May 2015 and March 2019 were reviewed. Children with congenital anomalies of the kidney or urinary tract other than VUR, a history of FUTI and/or VUR diagnosis before the study and missing data and/or a follow-up period <2 years were excluded from the study. The patients with findings supporting congenital renal dysplasia, such as loss of corticomedullary differentiation and renal hyperechogenicity on US, and with unscarred kidneys with a differential function <45% were not included.

Urine samples for culture were obtained from midstream urine. All of the patients underwent genital hygiene with soap and water in the laboratory before providing a urine sample. The diagnosis of FUTI was made on the basis of the presence of fever >38 °C with at least 100,000 colony-forming units/mL of a uropathogen cultured from the urine specimen and pyuria (leucocyte counts ≥5/high-power field).

In our Pediatric Nephrology Department, all patients underwent a renal US within two weeks of their first FUTI. The DMSA scan was performed at least six months after the diagnosis of FUTI in all patients. MCUG was performed on those patients with serious illness, septicemia, poor urine flow, raised creatinine, failure to respond to treatment with suitable antibiotics within 48 hours or infection with non-*E. coli* organisms, hydronephrosis, and/or other findings suggestive of VUR on ultrasound. Only those patients with complete radiological examinations were included in this study.

Hydronephrosis was defined using the Society for Fetal Urology's grading system (5). Abnormal US was defined by hydronephrosis, hydroureter (≥7 mm), parenchymal thinning, and dilatation of calyces.

Renal scarring was defined as a reduced or absent radionuclide uptake, a wedge-shaped defect, or the thinning or flattening of the renal outline. Reduced differential function (RDF) was defined as <45%. A kidney uptake of 45%-55% of the total renal activity was considered to be normal. The findings on DMSA scan were graded as mild (focal defect in uptake), moderate (uptake of renal radionuclide from 20%-40%), and severe (shrunken kidney with uptake less than 20%) (6). The DMSA scans were all evaluated by the same nuclear medicine specialist.

MCUG was performed at three to six weeks after the diagnosis of FUTI. VUR was graded according to the grading system of the International Reflux Study Committee. Grades 1-2 VUR were defined as mild VUR, while grades 3-5 VUR were defined as severe VUR. The pediatric radiologist and nuclear medicine specialist were unaware of the patients' clinical and laboratory findings.

Statistical Analysis

Statistical analyses were performed using SPSS version 11.0 (SPSS Inc, Chicago, IL). Values are expressed as a mean and standard deviation for continuous variables and as an interquartile range for qualitative variables. Qualitative variables were compared Ausing the chi-square test. A logistic regression analysis was performed to determine the association between the US findings and the DMSA scans in the presence of VUR. The sensitivity, specificity, positive predictive value, and negative predictive value (NPV) of US and late DMSA findings for VUR were calculated. A p-value <0.05 was considered significant.

Results

Demographic and Imaging Features of the Study Group

The records of 317 patients with a first febrile UTI were retrospectively reviewed in this study. The data of 97 patients who failed to meet the inclusion criteria were excluded from the study. The findings of the DMSA scan, renal US, and MCUG of the remaining 220 patients were analyzed. Figure 1 shows the flow of participant selection. The mean follow-up time was 3.9±1.37 years (range 2.54-5.27 years). The mean age of the patients was 4.3±2.07 years old (range 2-6.5 years). Of the 220 children, the female/male ratio was 1.53:1 (133 girls and 87 boys).

Abnormal US was determined in 130 patients. Hydronephrosis was the most common finding (n=86).

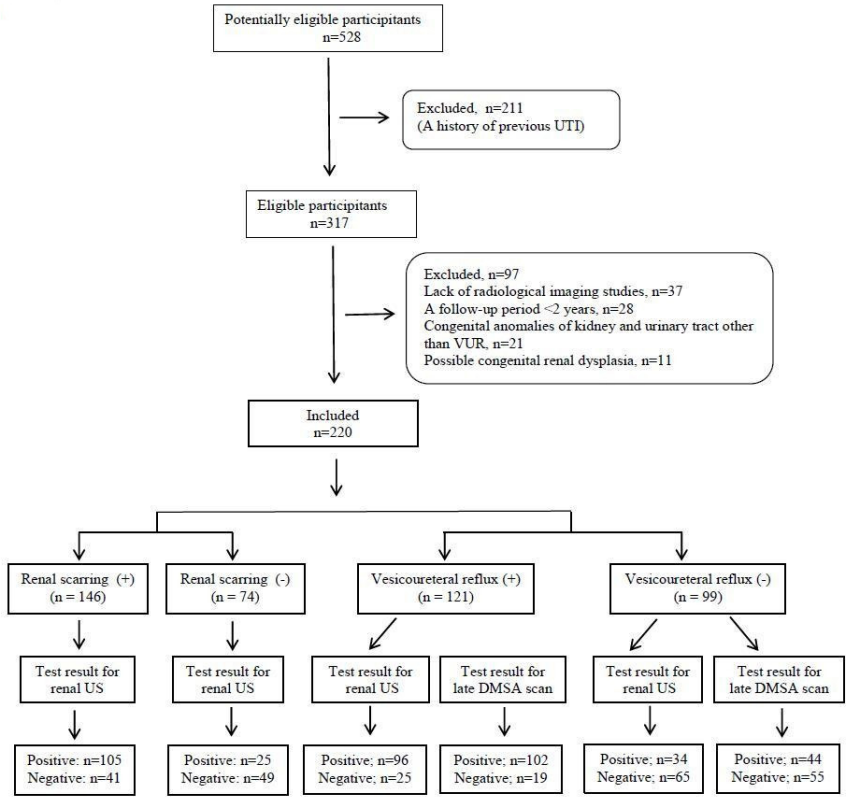

Figure 1. Participant selection diagram
VUR: Vesicoureteral reflux, UTI: Urinary tract infection, DMSA: Dimercaptosuccinic acid, US: Ultrasonography

Other US findings were as follows: hydroureter (n=69), caliectasis (n=60), and parenchymal thinning (n=58). In 121 of the 220 patients, VUR was determined (61 patients showed mild VUR, and 60 showed severe VUR).

The Relationship Between Late DMSA Scan and Renal US

Renal scarring was determined in 146 patients (44 had mild scarring, 79 had moderate scarring, and 23 had severe scarring). The frequency of abnormal US was higher in those patients with scarring than those without scarring (n=105 and n=25, respectively; p=0.011).

Parenchymal thinning was shown in 58 patients, all of them with renal scarring. The frequency of hydronephrosis was higher in those patients with renal scarring than in those without renal scarring (n=68 and n=18, respectively; p=0.026). The frequency of parenchymal thinning was higher in those patients with severe scarring than in those patients with mild and moderate scarring (n=15, n=16, and n=27, respectively; p=0.013).

The Renal Ultrasound and Late DMSA Scan Findings of the Patients with VUR

The frequency of abnormal US was higher in those patients with VUR than in those without VUR (p=0.009). Those patients with VUR had higher frequencies of parenchymal thinning, hydronephrosis, and hydroureter (p=0.000, p=0.022, p=0.000, respectively; Table I). Those patients with severe VUR had higher frequencies of both hydronephrosis and parenchymal thinning than those patients with mild VUR (p=0.022 and p=0.000, respectively; Table II). Twenty five (20.7%) patients with VUR (14 with mild VUR, and 11 with severe VUR) had normal renal US.

Both moderate and severe scarring were common in the presence of VUR (p=0.000 for both of them). Those patients with VUR had a higher frequency of RDF when compared to those patients without VUR (p=0.000; Table I). A significant difference was not determined between those patients with mild and severe VUR in terms of the degree of renal scarring and RDF (detailed results are shown in Table II).

Table I. The features of the patients with and without vesicoureteral reflux

	Vesicoureteral reflux (+) n (%)	Vesicoureteral reflux (-) n (%)	p-value
Gender (female)	76 (62.8)	57 (57.6)	0.758
Abnormal US	96 (79.3)	34 (34.3)	0.009
Hydronephrosis	66 (54.5)	20 (20.2)	0.043
Caliectasis	38 (31.4)	22 (22.2)	0.139
Parenchymal thinning	48 (39.7)	10 (10.1)	0.001
Hydroureter	61 (50.4)	8 (8.1)	0.000
Renal scarring	102 (84.3)	44 (44.4)	0.001
Severe scarring	18 (14.9)	5 (5.1)	0.000
Moderate scarring	61 (50.4)	18 (18.2)	0.000
Mild scarring	23 (19)	21 (21.2)	0.956
Reduced differential function	96 (79.3)	13 (13.1)	0.000

Values were expressed as number and proportion.
A p-value <0.05 was considered significant
US: Ultrasonography

Table II. The features of the patients with mild and severe vesicoureteral reflux

	Mild vesicoureteral reflux (+) n (%)	Severe vesicoureteral reflux (+) n (%)	p-value
Gender (female)	36 (59)	40 (66.7)	0.125
Abnormal US	47 (77.04)	49 (81.7)	0.392
Hydronephrosis	22 (36.1)	44 (73.3)	0.022
Caliectasis	17 (27.9)	21 (35)	0.857
Parenchymal thinning	8 (13.2)	40 (66.7)	0.000
Hydroureter	17 (27.9)	44 (73.3)	0.029
Renal scarring	47 (77.04)	55 (91.7)	0.046
Severe scarring	9 (14.8)	9 (15)	0.911
Moderate scarring	29 (47.5)	32 (53.3)	0.548
Mild scarring	9 (14.8)	14 (23.3)	0.106
Reduced differential function	44 (72.1)	52 (86.7)	0.094

Values were expressed as number and proportion.
A p-value <0.05 was considered significant
US: Ultrasonography

The Relationships Between Renal US, Late DMSA Scan, and the Presence/Grade of VUR

A logistic regression analysis showed a significant association between abnormal US and VUR or severe VUR (p=0.019 and p=0.011, respectively). Parenchymal thinning was associated with both VUR and severe VUR (p=0.038 and p=0.010, respectively). Renal scarring had a predictive value for VUR (p=0.005). While severe and moderate scarring were associated with the presence of VUR, there was no significant relationship between severe VUR and the degree of renal scarring. There was a significant association between RDF and VUR but not severe VUR (p=0.015 and p=0.242, respectively). Detailed results of the logistic regression analysis are shown in Table III.

The true and false positive/negative values and diagnostic accuracy of late DMSA scan and US to detect VUR and severe VUR are shown in Tables IV and V. Abnormal ultrasound had a sensitivity of 79.34% for VUR and 81.67% for severe VUR. The specificity of abnormal ultrasound was 65.66% for VUR and 70.63% for severe VUR. The NPV of abnormal US was 91.13% for severe VUR. Renal scarring on late DMSA scan had a sensitivity of 84.3% for VUR and 91.67 % for severe VUR. The NPV of renal scarring was 73.68% for severe VUR.

Discussion

The results of our study showed that parenchymal thinning and hydroureter were significant indicators for both the presence and degree of VUR in older children who had their first FUTI. There was a significant association between the presence of VUR and renal scarring and RDF on late DMSA scan. However, no relationship was found between the degree of renal scarring and different grades of VUR.

VUR is considered to be one of the most common urological anomalies that can predispose children to UTI. The incidence of VUR varies between 0.5% and 3% in healthy children, but the frequency of VUR rises to 30-64% in children with UTI (7,8). In our study, VUR was detected in 55% of patients who had their first FUTI. This result supports the need for more determining indicators to perform MCUG in children during their first FUTI so as to not miss a diagnosis of VUR.

An acute-phase DMSA scan has an important role in detecting parenchymal infection during active infection. Previous studies have shown that while the frequency of abnormal DMSA scan ranged from 51% to 73% during the acute period of FUTI, the frequency of permanent scarring

Table III. Logistic regression analysis showing factors associated with presence of vesicoureteral reflux and severe vesicoureteral reflux

	Vesicoureteral reflux			Severe vesicoureteral reflux		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Female gender	0.869	0.217-1,036	0.981	0.346	0.017-0.936	0.851
Abnormal US	1,549	1,215-5,541	0.019	1,417	1,153-6,439	0.011
Hydronephrosis	0.816	0.882-5,799	0.089	1,828	1,212-31,937	0.028
Caliectasis	0.522	0.575-4,936	0.341	0.191	0.156-2,650	0.459
Parenchymal thinning	1,130	1,058-7,415	0.038	2,175	1,692-45,761	0.010
Hydroureter	2,350	1,265-6,796	0.014	3,689	1,551-5,271	0.003
Renal scarring	2,317	1,624-9,174	0.005	1,216	1,108-1,471	0.043
Severe scarring	1,416	1,216-4,480	0.038	0.362	0.218-1,019	0.837
Moderate scarring	1,248	1,116-2,635	0.041	0.503	0.259-0.925	0.757
Mild scarring	0.415	0.172-1,109	0.691	0.215	0.127-0.815	0.947
Reduced differential function	1,420	1,324-12,936	0.015	0.386	0.025-2,550	0.242

A p-value <0.05 was considered significant
OR: Odds ratio, CI: Confidential interval, US: Ultrasonography

Table IV. The true and false positive/negative values for late DMSA scan and ultrasound to detect VUR and severe VUR

Test result	**VUR (+)**	**VUR (-)**	**Severe VUR (+)**	**Mild VUR**
Renal scarring	102	44	55	47
Positive	19	55	5	14
Negative	121	99	60	61
Abnormal renal ultrasound	96	34	49	47
Positive	25	65	11	14
Negative	121	99	60	61

VUR: Vesicoureteral reflux, DMSA: Dimercaptosuccinic acid

Table V. Diagnostic accuracy of renal bladder ultrasound and late DMSA scan to detect vesicoureteral reflux and severe vesicoureteral reflux

	Vesicoureteral reflux	**Severe vesicoureteral reflux**
Abnormal ultrasound		
Sensitivity (%)	79.34 (71.03-86.16)	81.67 (69.56-90.48)
Specificity (%)	65.66 (55.44-74.91)	70.63 (62.92-77.55)
+ Predictive value (%)	73.85 (67.94-79)	51.04 (44.35-57.69)
- Predictive value (%)	72.22 (64.07-79.13)	91.13 (85.65-94.65)
Renal scarring on late DMSA scan		
Sensitivity (%)	84.3 (76.57-90.27)	91.67 (81.61-97.24)
Specificity (%)	55.56 (45.22-65.55)	22.95 (13.15-35.53)
+ Predictive value (%)	69.86 (64.74-74.54)	53.92 (50.01-57.79)
- Predictive value (%)	74.32 (64.89-81.93)	73.68 (51.82-87.94)

DMSA: Dimercaptosuccinic acid

on the late DMSA scan was only 9.5%-11.9% (9,10). Studies have also reported a higher prevalence of permanent renal damage after acute pyelonephritis (11). Orellana et al. (12) showed that children older than one year had a higher frequency of renal scarring than infants. The frequency of permanent renal scarring was quite high (66.4%) in our patients who had their first FUTI. The high frequency of renal scarring might be due to the fact that we included older children in our study. In addition, differences such as type of imaging study, age at diagnosis, clinical presentation, and the distribution of the severity of VUR could affect the prevalence of renal scarring.

There is little consensus and little data on imaging after FUTI in older children (13). Hitzel et al. (14) suggest that MCUG is not necessary in children who have a normal US and DMSA scan. The revised guidelines by the Indian Pediatric Nephrology Group recommend DMSA scan as the first approach (followed by VCUG if positive) in children between the ages of one and five years after their first UTI (15). Doğan et al. (16) found that abnormal DMSA scan findings had a sensitivity of 83.87% for VUR in 32 children older than two years with recurrent UTI. However, their study included patients with urological abnormalities other than VUR, as well as children with bladder and/or bowel dysfunction (16). Balestracci et al. (17) investigated the predictive role of late DMSA scan for high-grade VUR in 122 children aged between 3 and 18 years with FUTI. They also included patients with FUTI which occurred before the

first year of life. Of their patients, 57.4% had an abnormal late DMSA scan. Abnormal late DMSA scan was associated with both VUR and high-grade VUR (17). We determined a sensitivity of 84.3% of the abnormal late DMSA scan for the presence of VUR. Our study included DMSA scan findings of patients with their first FUTI. We did not include patients with urological abnormalities other than VUR, or patients with bladder and/or bowel dysfunction or a history of FUTI before the study. Our results showed that abnormal late DMSA scan could predict the presence of VUR in older children who had their first FUTI.

Researchers have drawn different conclusions about the relationship between abnormal DMSA scan and severe VUR. Silva et al. (18) reported that severe VUR was associated with all subtypes of renal damage. In their study, the median age at diagnosis of the first UTI was 8.9 months, and the median age at diagnosis of VUR was 19 months. Interestingly, Jang et al. (19) showed that abnormal DMSA scan was more common in the presence of severe VUR in patients less than 1 year old. However, they could not show the same relationship in patients over 1 year old (19). Lee et al. (20) did not find a significant difference in the prevalence of renal scarring between the different grades of VUR in children between 0 and 5 years of age. In our study, late DMSA scan had a sensitivity of 91.67% for severe VUR. However, we did not identify a significant association between severe VUR and the degree of renal scarring.

The literature contains conflicting conclusions about the predictive value of renal US for VUR. Several studies found no significant association between US findings and the presence of VUR (21). Conversely, Darge (22) reported that cortical thinning, small kidneys, and cortical hyperechogenicity were associated with the presence of VUR. Doğan et al. (16) reported that renal US had a sensitivity of 75% for the presence of VUR. In the study by Balestracci et al. (17) of the 69 patients with normal renal US, 32 (46.3%) had VUR. In our study, abnormal US had a sensitivity of 79.34% for VUR; nevertheless, one-fifth of our patients with VUR had no abnormal US findings. Our results indicated that older children who had their first FUTI could have VUR even if renal US is normal.

There are also different opinions concerning the ability of US to detect the grade of VUR. Bayram et al. (23) reported that the frequency of abnormal US was higher in patients with grades 4-5 of VUR (18). Another study showed renal US had a sensitivity of 63%-86% in the diagnosis of severe VUR (19,24). Our results revealed that the sensitivity of abnormal renal US was 81.67%, and NPV was 91.13% for severe VUR. Based on the results of our study, normal renal US could indicate the absence of severe VUR in older children who have their first FUTI.

VUR is thought to be the most important risk factor for the development of renal scarring. However, recently, it has been suggested that UTI is more closely related to the development of permanent scarring than VUR (25). In our study, 44 patients had scarring but did not have VUR. This result might indicate that factors other than VUR, such as the severity of the inflammatory reaction, differences in the immunological system, and microbiological virulence factors, could play a role in the development of renal scarring.

Although renal US provides information about anatomic disorders of the kidney and urinary tract, several studies have shown that US is not a good determinant of renal scarring after the first UTI. Bush et al. (26) demonstrated that about one-fifth of children diagnosed with FUTI had renal scarring despite normal renal US. The false negative rate of renal US was 23% in children aged two years and older (21). Inversely, Merguerian et al. (27) found a significant correlation between renal US findings and diffuse renal scar, although there was a weak correlation between focal scar and renal US (22). In our study, about a third of patients with renal scarring had normal renal US. Accordingly, normal renal US cannot exclude the presence of renal scarring on late DMSA scan.

Study Limitations

This study has several limitations. First, this is a retrospective study with a small sample size. Second, our study could not distinguish whether DMSA scan abnormalities were congenital or acquired in patients without VUR. DMSA defects in these patients might be caused by congenital dysplasia, rather than UTI or VUR. Third, the reason for the high frequency of renal scarring might be related to possible previously undiagnosed infections. However, since this study was based on recorded medical data, we could not ascertain whether the symptoms of UTI had been present previously.

Conclusion

Our results showed that late DMSA scan findings were able predict the presence and grade of VUR in older children who had their first FUTI, and normal renal US was able predict the absence of severe VUR. However, older children who had their first FUTI should be investigated in terms of VUR after acute infection, even if renal scarring and abnormal renal US is not detected.

Ethics

Ethics Committee Approval: The protocol for the present study was reviewed and approved by the Institutional Review Board of Eskişehir Osmangazi University Faculty of Medicine (approval number: 25403353-050.99-E.110593).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.Ç., Design: N.Ç., A.K.T., Data Collection or Processing: N.Ç., Analysis or Interpretation: N.Ç., İ.A.S., N.A., Writing: N.Ç., A.K.T., İ.A.S., N.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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J Pediatr Res 2021;8(4):408-13
DOI: 10.4274/jpr.galenos.2021.67689

Original Article

The Risk Factors of Puberty Precocious in Girls: Is the Condition Related with Polychlorobiphenyls?

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ABSTRACT

Aim: Our aim was investigate the effect of polychlorobifenyls (PCBs) and other factors on puberty precocious (PP) in girls were diagnosed with idiopatic PP and premature thelarche (PT).

Materials and Methods: The study group included 50 girls aged between 2-8 years old with PP and PT. The control group included 50 healthy girls with same age range and no puberty findings. Data was collected in terms of breast and pubic hair stages, weight, height, body mass index (BMI), standard deviation scores (SDSs), location of residence, gestational age and maternal age at menarche (AAM). Twenty-one PCB levels were evaluated in serum and urine. One-Way ANOVA test was used for comparison between the groups. For subgroup analysis, Mann-Whitney U test, multiple regression analysis were used.

Results: The mean age of the study and control groups were 6.70±1.20 and 5.23±1.25 years, respectively. The studied PCBs were not detectable found in either the study or the control groups. The BMI SDSs of the patients in study and healthy groups were 0.49±1.09 and -0.12±1.28, respectively (p=0.1). Weight SDSs in the study group were found to be significantly higher than healthy group (0.72±1.35 vs -0.20±1.47, p=0.008 Maternal AAM of the patients in study group was significantly lower (p=0.006). In study group 98% of the patients were living in down town and district, whereas this ratio was 92% in control group (p=0.024). In study group 29 patients (58%) were diagnosed with PT. Basal follicle stimulating hormone and estradiol levels, bone age and uterine longest axis dimensions results were significantly different.

Conclusion: We found that studied PCBs don't influence on PP in girls aged between 2-8 years old. However, weight SDS, maternal AAM, location of residence of the patients had a significant role on PP in this patient population.

Keywords: Puberty precocious, premature thelarche, environmental endocrine distrubs, polychlorobifenyl, obesity

Introduction

Over the last century, it has been seen that the age of onset of puberty has tended to shift earlier. Sorensen et al. (1) have argued that the age of onset of breast development in America has shifted earlier. Central precocious puberty (CPP) occurs as a result of the early activation of the hypothalamus-pituitary-gonad axis and is characterized by the development of secondary sex characteristics in girls before the age of eight (2). Although it is thought that there are many reasons for this, genetic factors, nutritional differences, ethnic origin, environmental factors, and exposure to endocrine disruptors are among the common causes (3,4).

Endocrine disruptors, being one of the causes of CPP, can alter the production, transport, destruction and excretion

***Poster Presentation: 57th Annual ESPE 2018 Meeting 27-29 September in Athens, Greece (335-P2).**

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Received: *26.10.2020* **Accepted:** *30.01.2021*

of endogenous hormones and even alter their effects on the target cell. One or more of these effects may also occur together. Exposure can occur transplactentally during the prenatal period, with breast milk in infancy, through inhalation and digestion in childhood, or due to industrial accidents (5). Polychlorinated biphenyls (PCBs), being one of these chemicals, are theoretically constituted of 209 different types of chemical and aromatic compounds that are formed by binding different numbers of chlorine ions in different configurations on a biphenyl structure. They can also be found in synthetic and industrial products. PCBs have been used as organic diluents, softeners, pesticide extenders, adhesives, dust reducers, cutting oils, flame retardants, heat transfer fluids, dielectric fluids for transformers and capacitors, hydraulic lubricants, sealants and in carbonless copy paper. A significant portion of the environmental burden of these compounds is due to careless disposal practices, accidents, leakage from various industrial plants, and chemical waste disposal sites (6). Most of these compounds are lipophilic and have a long half-life. As a result, they accumulate in adipose tissue in living creatures and long-term exposure, even at low levels, may cause chronic toxicity (7). As humans rank high in the food chain at the trophic level, they accumulate high concentrations of these pollutants in lipid tissues and may become more vulnerable to their toxic effects (8).

The main purpose of this study was to analyse the effect of twenty PCB groups, namely; PCB 8, PCB 20, PCB 28, PCB 35, PCB 52, PCB 77, PCB 81, PCB 101, PCB 105, PCB 114, PCB 118, PCB 123, PCB 126, PCB 138, PCB 153, PCB 156, PCB 157, PCB 167, PCB 169 and PCB 189 on PP in girls with the diagnosis of PP or premature thelarche (PT) in our Paediatric Endocrinology Outpatient Clinic. Furthermore, the relationship between PP and the other possible factors such as weight, height, body mass index (BMI), gestational age at birth and maternal age at menarche (AAM) and the residence location of the patients were investigated.

Materials and Methods

The study was conducted after approval was given by the Ethics committee of Ege University Faculty of Medicine (date: 29.12.2015, approval no: 15-11/4).

The study group (group 1) included 50 girls aged between 2 and 8 years old with a diagnosis of idiopathic PP or isolated PT in a single Paediatric Endocrinology Outpatient Clinic. The control group (group 2) included 50 healthy girls with the same age range in the same centre who were admitted to the same department for their routine check-ups and had previously had no chronic disease or evidence of puberty signs.

In the investigation of patients with precocious puberty, their anthropometric measurements and clinicodemographic characteristics were evaluated, and the Tanner stages of the patients were identified. Serum and urine samples were obtained from each patient in order to determine PCB levels. Bone age (BA) (according to the Greulich-Pyle BA atlas), ovarian and uterus sizes, morning basal luteinizing hormone (LH), follicle stimulating hormone (FSH), and estradiol (E2) serum levels were recorded from the files of the patients in group 1. In pelvic ultrasonographic imaging of the patients, cases with ovaries whose longest axis was 2.5 cm or 1 cm^3 in volume from the ovarian dimensions were accepted as being in adolescence, cases with a long axis exceeding 3.4 cm from the uterine dimensions or with an endometrial echo exceeding 2 mm were accepted as being in adolescence (9). Basal FSH, LH, E2 levels were measured in the serum sample by electrochemiluminescence immunoassay method using Roche Diagnostic GmbH (Germany) kits in a Modular Analytics E170- Roche Diagnostic GmbH (Germany) device. In these kits, measurement ranges are given as 0.01-200 mIU/mL for LH and FSH and 5.0-4,300 pg/mL for E2. Basal LH values >0.6 mIU/mL were accepted as true PP. Basal E2 levels above 12 pg/mL were considered higher than the age group (10). Those patients with isolated PT had glandular breast tissue on palpation (as opposed to lipomastia). Their BA corresponded with their chronological age, basal and GnRH-stimulated gonadotropin levels were normal and other signs of puberty such as pubarche and menarche were absent in contrast to those patients with precocious puberty.

Both groups were assessed based on the patients' gestational ages, and location of residence. Preterm birth was determined as being born before the 37th week, and term-birth was determined as having a birth age between 37 and 40 weeks. The location of residence was classified as urban or rural. Maternal AAM, mean BMI and mean weight standard deviation scores (SDSs) of the groups were also compared.

Serum and urine samples of all patients included in the study were stored at -80 °C until they were analysed. Serum and urine PCB measurements were made at Ege University Drug Development and Pharmacokinetics Research Application Centre. For PCB analysis, serum samples were studied by the gas chromatography mass spectrometry (GC-MS) method on a Shimadzu GC-MS QP-2010 Plus (Japan) device. Restek CL Pesticides 2 (20 m, 0.18 mm i.d. 014 µm film thickness) was used as the column. The column temperature was initially increased from 120 °C to 200 °C at a rate of 45 °C/min. Then it was increased to 230 °C at a

rate of 15 °C/minute, and finally to 300 °C at a rate of 30 °C/minute and then kept constant for 3 minutes. For the study, 1 mL of serum was put into a glass tube and 9 mL of type 1 water was added. Solid-phase extraction (SPE) cartridges were lined up in the manifold. Five mL of methanol, 5 mL of methyl-tert-butyl ether (MTBE) and 3 mL of type 1 water were passed through the cartridge, respectively. The serum sample was then loaded into the SPE cartridge. The sample flow rate was set at 6-8 mL/minute. After passing the sample, the cartridge was washed with 3 mL of type 1 water and dried under vacuum for 10-15 minutes. The extract collected at the bottom was discarded and a clean glass tube was placed in the manifold. Collection was done with 5 mL MTBE. After the collected extract was evaporated to dryness under nitrogen at 40 °C bath temperature, 1 mL n-Hexane was added to the tube and mixed by vortex. It was filtered through 0.45 m polytetrafluoroethylene filter and put into a vial and injected into the GC-MS system.

Using the Quechers kit for PCB analysis in urine samples; 5-10 g of the sample was weighed. It was put into a 50 mL Teflon tube. Ten mL of 1% acidified acetonitrile (with acetic acid), containing 100 ng/g Aldrin standard (internal standard) was added to the sample. The mouth of the tube was tightly closed and shaken by hand for about 1 minute. Ready mix containing 6 g magnesium sulphate (MgSO4) and 1.5 g sodium acetate (CH3COONa) was added to the sample. The mouth of the tube was tightly closed and shaken by hand for about 1 minute. It was then mixed by high-speed vortex for 5 minutes. It was centrifuged for 5 minutes at 4,000 rpm. Liquid Extract was transferred to a 10 mL ready-made tube containing 2-8 mL of 400 mg primary secondary amine and 1,200 mg of MgSO4. The mouth of the tube was tightly closed and shaken by hand for about 1 minute. It was then mixed by high-speed vortex for 5 minutes. It was centrifuged at 4,000 rpm for 5 minutes. It was filtered from the upper phase to the vial and delivered to GC ECD/GCMS devices.

The studied PCBs in laboratory tests were as follows: PCB 8, PCB 20, PCB 28, PCB 35, PCB 52, PCB 77, PCB 81, PCB 101, PCB 105, PCB 114, PCB 118, PCB 123, PCB 126, PCB 138, PCB 153, PCB 156, PCB 157, PCB 167, PCB 169 and PCB 189. The qualitative and quantitative results were evaluated. For quantitative measurements, any PCB levels higher than 0.005 mg/kg were noted.

Statistical Analysis

The statistical analyses were performed using SPSS version 16.0. The One-Way ANOVA test was used for comparisons between groups. For subgroup analysis, Mann-Whitney U test and multiple regression analysis were used. A p-value <0.05 was accepted as statistically significant.

Results

In group 1 (n=50), the mean age was 6.7±1.2 years. In group 2 (n=50), the mean age was 5.23±1.25 years. When the anthropometric measurements were compared, the weight SDS in group 1 was 0.72±1.35, the height SDS was 0.77±1.40, the BMI SDS was 0.49±1.09. In group 2, the weight SDS was -0.20±1.47, the height SDS was -0.35±1.54, and the BMI SDS was found to be -0.12±1.28. While there was no difference between group 1 and group 2 in terms of height and BMI SDS, the weight SDS in group 2 were found to be significantly higher than group 1 (p<0.05) (Table I).

When the relationship between the time of birth (preterm or term) and the onset of puberty was evaluated, it was observed that the rate of delivery on time was 88% in group 1 and 84% in the healthy control group. It was observed that the preterm birth rate was 12% in group 1 and 16% in the healthy control group. There was no statistically significant difference in delivery time between children entering early puberty and those in the healthy control group (p>0.05).

Maternal AAM (years) were 12.06±1.25 in group 1 and 12.65±0.92 in group 2 (p=0.006). It was determined that the age of onset of maternal menarche was statistically significantly earlier in group 1 than in group 2 (p<0.05) (Table II).

When the relationship between professions of the

Table I. Anthropometric measurements of the groups

	Study group (n=50)	Control group (n=50)	p-value
Weight SDS	0.72±1.35	-0.20±1.47	**0.008**
Height SDS	0.77±1.40	-0.35±1.54	0.12
BMI SDS	0.49±1.09	-0.12±1.28	0.1

BMI: Body mass index, SDS: Standard deviation score

Table II. The relationship between puberty precocious, premature thelarche and gestational age at birth and maternal menarche age

	Study group (n=50)	Control group (n=50)	p-value
Maternal menarche age	12.06±1.25	12.65±0.92	0.006
Premature born (%)	12	16	
Term born (%)	88	84	0.56

mothers and fathers of both groups and the time of onset of puberty was examined, it was seen that 58% of the mothers in group 1 were housewives, 24% were self-employed and 18% were civil servants, 66% of fathers were self-employed and 34% were civil servants. In group 2, 74% of the mothers were housewives, 14% were self-employed, 12% were civil servants, and 2% of fathers were unemployed, 78% were self-employed and 20% were civil servants. No statistically significant difference was found between family professions and the onset of puberty (p>0.05).

When birth weights were examined, the mean birth weight of group 1 was 3,180 gr ±664 and the mean birth weight of group 2 was 3,048 gr ±641. There was no significant difference between group 1 and group 2 in terms of birth weight (p=0.748).

The distribution of pubic hair growth and breast development stages according to Tanner at the time of admission in the girls were determined such that, in group 1, 28% of patients (n=14) were in pubarche stage 2, 60% of patients (n=30) were in pubarche stage 3, 10% of patients (n=5) were in pubarche stage 4, and 2% of patients (n=1) were in pubarche stage 5. 8% (n=4) were in thelarche stage 2, 64% of patients (n=32) were in thelarche stage 3, 20% of patients (n=10) were in thelarche stage 4, and 8% of patients (n=4) were in thelarche stage 5. At the time of application, delta BA of these patients was determined to be 0 in 22% (n=11) of patients, 1 in 32% (n=16) of patients, 1.5 in 16% (n=89) of patients, 2 in 28% (n=13) of patients, 3 in 2% (n=1) of patients, and 4 in 2% (n=1) of patients.

CPP and Isolated PT Subgroups Results

Twenty-nine out of 50 patients (58%) in Group 1 were diagnosed with isolated PT, and 21 patients (42%) were diagnosed with CPP. Anthropometric measurements were compared, the weight mean SDS in the CPP group was 0.89±1.43, height SDS was 0.88±1.47, and BMI SDS was 0.71±1.05. In isolated PT, weight SDS was -0.49±1.22, height SDS was 0.63±1.31, and BMI SDS was found to be 0.19±1.10. There was no difference between the PP group and PT group. (p>0.05) (Table III).

Maternal AAM (years) were 11.9±1.2 in the PP group and 12.2±1.3 in the PT group (p=0.076). It was determined that maternal AAM was not statistically significantly (p>0.05).

The laboratory tests for differentiating precocious puberty from PT are BA, basal LH, FSH, E2 levels, pelvic ultrasonographic imaging of the ovaries and uterine longest axis and volume dimensions. BA was 1.48±0.83 in the CPP group and 0.85±0.77 in the isolated PT group (p=0.015).

Table III. Anthropometric measurements and laboratory values of CPP and isolated PT patients'

	CPP group (n=21)	Isolated PT group (n=29)	p-value
Weight SDS	0.89±1.43	0.49±1.22	0.29
Height SDS	0.88±1.47	0.63±1.31	0.53
BMI SDS	0.71±1.05	0.19±1.10	0.97
Basal LH (mIU/mL)	1.01±1.38	0.53±0.78	0.10
Basal FSH (mIU/mL)	3.53±1.88	2.42±1.74	**0.016**
Basal E2 (pg/mL)	18.4±14.4	8.76±18.4	**0.00**
Uterine longest axis (mm)	36.9±8.28	29.8±10.4	**0.006**
Right ovarian longest axis (mm)	25.2±8.3	24.2±8.7	0.45
Volume of right ovary (cm^3)	4.18±4.7	4.85±6.9	0.52
Left ovarian longest axis (mm)	24.0±7.1	20.6±6.47	0.14
Volume of left ovary (cm^3)	3.03±3.3	2.47±2.2	0.52
BA	1.48±0.83	0.85±0.77	**0.015**

BA: Bone age, BMI: Body mass index, CPP: Central puberty precocious, E2: Estradiol, FSH: Follicule stimulating hormone, LH: Luteinizing hormone, PT: Prematury telarche, SDS: Standard deviation score

This result is statistically significantly (p<0.05). Uterine longest axis was 36.9±8.28 in the CPP group and 29.8±10.4 in the isolated PT group. Basal FSH (mIU/mL) in the CPP group was 3.53±1.88 and 2.42±1.74 in the isolated PT group (p=0.016). Basal E2 (pg/mL) in the CPP group was 18.4±14.4 and 8.76±18.4 in the isolated PT group (p=0.00). The CPP and the isolated PT subgroups basal FSH, E2 levels, BA and uterine longest axis dimensions results were statistically significantly (Table III).

We were unable to demonstrate any quantifiable levels of PCB remnants in the serum and urine samples of the patients in either group.

Discussion

Our results demonstrated that the patient's location of residence, maternal AAM and their weight had a significant role on PP in those girls aged between 2 and 8 years old. However, we were unable to demonstrate an association between PP and PCBs we studied or any other factors.

As far as we know, in the studies conducted so far, no relationship has been found between PCB exposure and

early puberty in girls. In one study conducted to evaluate intrauterine PCB exposure, they found no relationship between 6 PCB congeners (118, 138, 153, 156, 170, 180) and menarche age and menstrual cycle length in 436 Danish girls at an average age of 19.6. They also demonstrated 14% shorter menstrual cycle times in girls exposed to high doses of 2 PCB congeners in comparison to those exposed to low doses (11). In another study conducted with 192 healthy 9-year-old girls living in New York, Wolff et al. (12) argued that PCB exposure had no effect on breast development and that breast development could be delayed in the group with high PCB exposure and low BMI. In another study, Su et al. (13) reported significantly lower E2 concentrations in eight-year-old children exposed to high levels of Polychlorinated Dibenzo-p-Dioxins and Polychlorinated Dibenzofurans (PCDD/Fs) and PCBs. Moreover, they demonstrated a significant association between PCBs median exposure level and fundus length after adjusting for BA. They concluded that in utero exposure to PCBs resulted in decreased serum E2 concentrations and this was thought to delay the reproductive development of these girls. They also observed a borderline significant effect of exposure level on breast and Tanner stages and found that there was a significant relationship between PCBs median exposure level and fundus length after adjusting for BA (13). Gellert (14) demonstrated that the estrogenic activity of a PCB was associated with decreased neuroendocrine differentiation and premature reproductive aging. Denham (15) showed that prepubertal PCB exposure caused menarche age to occur earlier in girls. In contrast, Vasiliu et al. (16) and Yang et al. (17) showed that PCB exposure in the prenatal and early postnatal period did not affect the age of menarche and pubertal development in girls.

In our study, no PCB residue was found in either group. Therefore, the relationship between PCB exposure and early puberty was not evaluated. The insufficient number of patients can be shown primarily among the reasons for not being able to determine a relationship between precocious puberty and PCB exposure. However, although PCB exposure has an effect on the early onset of puberty, the amount of PCBs may have been reduced to immeasurable levels due to the cross-sectional nature of the study. The individuals in the study group live in and around Izmir. The fact that the industrial establishments in this region have relatively less effect on the formation of PCBs can be considered as another reason why PCBs were not found in the serum samples of the patients. In addition, another limitation of this study is whether the individuals' living spaces were in industrial areas or not. It is thought that meaningful results may be found if they lived in industrial areas which could lead to PCB contamination.

In our study, the weight SDS of the group with early adolescence was found to be significantly higher. However, there was no significant difference between BMI. In the past decades, obesity has become a major health problem in childhood. Obesity can also cause a number of short-term and long-term metabolic disorders including cardiovascular diseases. In addition, it can affect the onset of puberty (18). Several studies have demonstrated that an earlier onset of puberty is associated with obesity in girls. It is known that a certain amount of body fat is a necessity for normal reproductive function. However, increased adipose tissue is a risk factor for pubertal disorders (19,20). Early maturation nearly doubled the odds of being overweight in girls participating in the US National Longitudinal Study of Adolescent Health (21). Slora et al. (22) reported that BMI is significantly associated with the onset of puberty since heavier children reach puberty earlier. Two of the mechanisms suggested to explain the relationship between BMI increase and precocious puberty are high leptin levels and insulin resistance mechanisms. Leptin is a hormone that originates in the adipose tissue and it is essential for normal puberty development. In studies, low leptin levels and delayed puberty were found in girls with less than normal adipose tissue (23). In a study conducted by Matkovic V et al. (24) regarding leptin levels above 12 ng/mL, it was found that every 1 ng/mL increase in leptin level shifts the age of menarche 1 month earlier. However, leptin and insulin levels were not studied in our study.

In the current study, there was an association between PP and maternal AAM and the location of patient's residence. The mean age of maternal menarche was significantly lower in those patients with PP. In concordance, Durand et al. (25) confirmed the high incidence of affected girls with familial early puberty. The mode of inheritance of the phenotype was predominantly maternal. Furthermore, they found that the maternal AAM of the girls with the familial form of CPP was significantly lower than in those with sporadic forms. In addition, we found that those girls living in urban areas carried a significantly higher risk of PP. Similarly, in a study by Ma et al. (26), it was noted that urban Chinese girls were experiencing earlier breast development than the current norm.

Study Limitations

Our study has some limitations. First of all, the size of the study population was low. The second limitation was that it only consisted of patients from a limited area, and therefore did not reflect a wide geographic region. In addition, we could only investigate 20 PBCs. These might explain why we could not detect any of the PCBs in the samples of our patients.

Conclusion

In conclusion, we demonstrated that PCBs we studied do not have an influence on PP in girls aged between 2 and 8 years old. However, living in an urban area, having a higher weight and a lower age of maternal menarche had a positive effect on PP in girls aged between 2 and 8 years old. In order for the endocrine disruptors to show their effects, the time, length and amount of exposure are important. We can conclude that exposure to PCBs in our region is not enough to have any effects on puberty.

Ethics

Ethics Committee Approval: The study was conducted after approval of the Ethics comittee of Ege University Faculty of Medicine (approval date: 29.12.2015; approval no: 15-11/4).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Design: Ş.D., Data Collection or Processing: R.B.G.B., S.Ö., Ö.K., Ş.D., Writing: R.B.G.B., R.D.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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J Pediatr Res 2021;8(4):414-23
DOI: 10.4274/jpr.galenos.2021.29963

Original Article

The Effect of Food Addiction in Children on Obesity: A Systematic Review and Meta-Analysis Study

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ABSTRACT

Aim: This study aimed to analyse the effect of food addiction in children on obesity.

Materials and Methods: A comprehensive literature review was conducted between January 2013 and July 2019 (Google Scholar, Pubmed, Embase/Elsevier, PsycINFO, EBSCOhost, Science Direct, BioMed Central). The word combinations "child", "adolescent", "obesity", "food addiction", "eating behaviour" and "food addiction scale for children" were used in the search process. The selected articles were examined in detail by two independent reviewers, and the methodological quality of the studies to be included in this study were evaluated using the Joanna Briggs Institute Meta-Analysis Statistical Appraisal and Review Tool (JBI-MAStARI Critical Appraisal Tool). General effect size, tests of heterogeneity, publication bias, and sensitivity analyses were performed with the random-effects model. The Comprehensive Meta-Analysis 3 software package was used for data analysis.

Results: As a result of the test of heterogeneity, those studies falling within the food addiction in children sub-dimension were determined to show heterogeneous characteristics ($Q=74,109$, $I^2=83.80$, $p<0.01$). The result of the publication bias test indicated the presence of publication bias. The overall effect size value of all studies, which was found using the random-effects model, was determined to be 0.346 [95% confidence interval (CI)], a value between the 0.152-0.539 CI. According to the results, food addiction was found to have a positive and moderate effect size on obesity when the average effect sizes within a 95% CI were considered. Accordingly, food addiction was determined to significantly affect obesity in children ($p<0.05$).

Conclusion: In this study, food addiction in children was determined to affect the prevalence of obesity in children.

Keywords: Child, adolescent, obesity, food addiction, systematic review, meta-analysis

Introduction

With the increase in the prevalence of childhood obesity across the world in recent years, food addiction has increasingly taken our attention as it is one of the factors affecting obesity (1-3). Food addiction is based on the idea that certain processed, high-calorie, and palatable foods may have addictive potentials and that excessive consumption of these foods can lead to addiction-like behaviours (4,5). How these foods lead to addiction-like eating behaviour is already being debated. It has been suggested that especially processed, high-calorie, and palatable foods rich in sugar, fat, starch, and salt increase the desire to eat by stimulating the reward systems in the

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Received: *21.11.2020* **Accepted:** *07.01.2021*

brain more when compared to other foods and lead to a loss of control over eating behaviour (6,7). With this loss of control over eating behaviour, the desire for addictive foods increases and the desire for healthy food intake decreases, thus increasing the rates of addictive food consumption (6-8). This leads to obesity through the intake of more calories in children (1,9,10).

Despite growing evidence of food addiction among adults, little is known about the role of food addiction in childhood obesity. As developmental stages continue in children, they may be more affected by these addictive foods (6). In one study, the most addictive foods were found to be chocolate, French fries, sugar, ice cream, carbonated drinks, rice, pasta, chips, and white bread (11). In another study of 50 children aged between 8 and 19 years, Merlo et al. (9) determined that 15.2% of children with overweight or metabolic diseases had food addiction. Food addiction has been found to be largely associated with overeating, uncontrolled eating, emotional eating, over-engagement in food, body sizes, and over-engagement in calorie calculation and control (9). In their study on 150 children between the ages of 5-12 years, Burrows et al. (12) found food addiction at a rate of 22.7%. Food addiction in children has been found to be significantly associated with high body mass index (BMI) scores (12). In a study of 801 adolescents aged between 11 and 18 years, Ahmed and Sayed (13) found food addiction to be 15.7%. Siah et al. (14) found no significant relationship between food addiction and BMI in adolescents. The e-literature indicated that the majority of the studies associating food addiction with obesity in children were studies conducted on children diagnosed with obesity (11,15,16). There are very few comparative studies on how food addiction affects obesity in children who are healthy and who are obese (15,16).

This diversity of these study results, which are already scarce in the literature, makes it difficult to reach a clear conclusion on this subject. These differences in results require re-analysis of the study results with advanced analysis techniques. The best-known statistical method is systematic review and meta-analysis (17,18). However, although systematic reviews and meta-analyses have been conducted throughout the world regarding food addiction involving adults and children, no systematic reviews and meta-analyses have been found to explain the effect of food addiction on obesity in children (19,20). This constituted the main starting point of this study. This study aimed to synthesize the results of studies investigating the effects of food addiction in children on obesity by using systematic review and meta-analysis methods.

Materials and Methods

Literature Review

Since no systematic review and meta-analysis studies on this subject were found in the world literature, the starting time of the review was chosen as 2013, when the food addiction scale was first developed. Accordingly, the literature review aimed to access studies between January 2013 and July 2019. In the preparation of the systematic review and meta-analysis, the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement) criteria were taken as a base (21). During the data collection phase, studies whose full text could be accessed were included in this study. In the data collection process, seven electronic databases including BioMed Central, Pubmed, Science Direct, PsycINFO, EBSCOHost, Embase/Elsevier and Google Scholar were reviewed.

Review Strategy

The keywords were generated based on the research question. MeSH (Medical Subjects Headings) was utilized for generating the English keywords, while the content of the Turkey Science Terms web page was used to find the Turkish equivalent of the English keywords. During the online search, keywords "child", "adolescent", "obesity", "food addiction", "eating behaviour", and "food addiction scale for children" and their Turkish equivalents were used. The PICO format was employed to design the research question in the meta-analysis. This format corresponds to the research question population (P: population), intervention (I: intervention), comparison groups (C: comparison), and results (O: outcomes). The PICO format of our study was as follows: when studies investigating the effect of food addiction in children on obesity were reviewed, the target population of our study was identified as those studies sampling children and adolescents with obesity around the world as the study population (population). The intervention under the PICO acronym was determined as food addiction, while the comparison criterion was determined as healthy children and adolescents. As for outcomes, this criterion referred to children with obesity who had food addiction and healthy children with food addiction.

The Selection of the Studies

The criteria for including the studies accessed as a result of the review in this study were as follows: a) the study should have a sample range aged between 4 and 21 years; (b) the design of the study should be randomized controlled, quasi-experimental, cross-sectional, case-control, cohort, or similar; (c) variables should include BMI; (d) it should have

adequate statistical data; and (e) it should employ a valid and reliable food addiction scale for children. On the other hand, the exclusion criteria included duplication, non-inclusion of the BMI variable, and sampling a different population. The selection of the studies for meta-analysis was carried out independently by two researchers. A comparison of the selected studies indicated a 100% agreement. Studies included in the analysis were arranged under the "PRISMA Flow Diagram" directives, and the flow diagram showing the reduction of 13,646 studies accessed as a result of the review to 13 studies included in the meta-analysis (PRISMA 2009 Flow Diagram) is presented in Figure 1 (21).

Evaluation of the Studies in Terms of Methodological Quality

The methodological quality of each study was evaluated with the Joanna Briggs Institute Meta-Analysis Statistical Appraisal and Review Tool (JBI-MAStARI critical appraisal tool), which was translated into Turkish by the researcher (22). The Joanna Briggs Institute classifies quantitative research designs into three groups including (1) experimental/quasi-experimental, (2) observational, and (3) descriptive. The checklists developed accordingly are of three types and include a set of evaluation criteria or questions related to research designs. The items on the checklist are generally intended to assess the four types of bias in studies. These are selection bias, performance bias, detection bias, and attrition bias. For each item in the JBI-MAStARI checklists, a "Yes" response is assigned 1 point, while responses such as "No", "Not specified", or "Not appropriate" are assigned 0 points. The JBI-MAStARI critical appraisal score ranges from 0-8. The higher the total score is, the higher the methodological quality of the study is (22). As a result of the evaluation, some studies were determined to be scored between 5 and 8, and their research quality was evaluated to be medium or high. A summary of the methodological quality appraisal of the studies is presented in Table I.

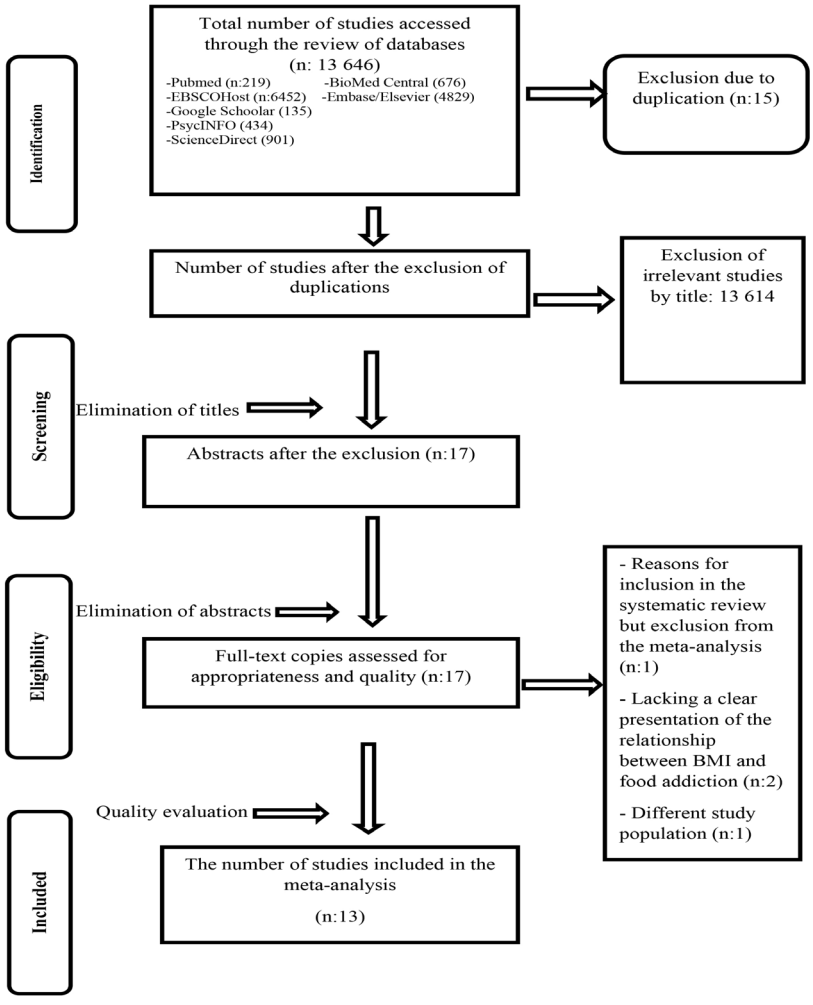

Figure 1. Flow diagram for the selection of the studies

Table I. A summary of the methodological quality appraisal of the studies investigating the effect of food addiction in children on obesity

Studies	Were the criteria for inclusion in the sample clearly defined?	Were the study subjects and the setting described in detail?	Was the exposure measured in a valid and reliable way?	Were objective and standard criteria used for the measurement of the condition?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were the outcomes measured in a valid and reliable way?	Was an appropriate statistical analysis used?	Total Score
Keser et al. (11)	U	Y	Y	Y	U	U	Y	Y	5
Burrows et al. (12)	U	Y	Y	Y	U	U	Y	Y	5
Ahmed and Sayed (13)	Y	Y	Y	Y	U	U	Y	Y	6
Siah et al. (14)	Y	Y	Y	Y	U	U	Y	Y	6
Meule et al. (15)*	U	Y	Y	Y	U	U	Y	Y	5
Tompkins et al. (16)*	Y	Y	Y	Y	U	U	Y	Y	6
Borisenkov et al. (23)	N	U	Y	Y	Y	Y	Y	Y	6
Mies et al. (24)	Y	Y	Y	Y	Y	Y	Y	Y	8
Richmond et al. (25)	Y	Y	Y	Y	Y	Y	Y	Y	8
Rodrigue et al. (26)	Y	Y	Y	Y	Y	Y	Y	Y	8
Zhao et al. (27)	N	Y	Y	Y	Y	Y	Y	Y	7
Naghashpour et al. (28)	Y	Y	Y	Y	Y	Y	Y	Y	8
Filgueiras et al. (29)	Y	Y	Y	Y	Y	Y	Y	Y	8

Y= Yes, N= No, U= Unclear, NA=Not applicable
*Evaluated according to experimental research

Statistical Analysis

In this study, the group difference method was employed in the analysis of the data. Data were analysed using the Comprehensive Meta-Analysis software (CMA 3.0). "Hedges' g" was used to calculate the effect size (17,30). Cooper (30) classified the effect size as follows: d≤0.20 is considered as weak, d<0.80 as moderate, and d≥0.80 as big effect size (17). Cohen's effect size classification was used in this study. The fixed or random effects models are used according to heterogeneity analysis (17). The random effect model was used in this study (17). Cochran's Q statistic, p-value, and I^2 tests were used to test the heterogeneity of effect sizes. At the significance phase of the Q test, the limit value for the p-value is recommended to be 0.10. In the evaluation of heterogeneity, if the heterogeneity ratio (I^2) is less than 25%, then there is no heterogeneity; between 25-50%, it is low; between 51-75%, it is moderate, and above 75%, it is considered to be high (31). Funnel plot graph, Rosenthal and Orwin's fail-safe N, Duval and Tweedie, Egger regression, and Begg and Mazumdar correlations were used for the analysis of publication bias (17). The significance level was accepted as 0.05.

At the outset, ethics committee approval was obtained from Dokuz Eylül University, Non-Interventional Research Ethics Committee (IRB: 2019/20-14). Since this was a meta-analysis study, no study was conducted on children and their parents. For this reason, it was not necessary to get permission from the children or their parents.

Results

The systematic review included 17 studies, while the meta-analysis involved 13 studies. Four studies were excluded from the sample because they did not contain the necessary data for the meta-analysis. The sample of the study consisted of children and adolescents aged between 4 and 21 years. The studies included in the systematic review and meta-analysis covered studies conducted between 2013 and 2019. The characteristics of the studies included in the systematic review and meta-analysis are shown in Table II.

Table II. Systematic summary of studies on the effect of food addiction in children on obesity

Author-Year of the study	Country	Research design	Sample size	Measuring tools	Major findings
Keser et al. (11)	Turkey	Cross-sectional study	100	Food addiction scale Socio-demographic/ anthropometric measurements	71% out of 100 children with overweight and obesity were found to have food addiction, which shows that food addiction plays an important role in childhood obesity
Burrows et al. (12)	United States of America	Cross-sectional study	150	Food addiction scale, Child feeding questionnaire, Socio-demographic/ anthropometric measurements	Food addiction in children was significantly associated with high BMI z scores. The mean scores of food addiction showed a statistically significant increase from thin to overweight and obese groups (2.9%, 14.7%, 32.3%, respectively). Mean addiction scores of normal weighted subjects were found to be 50%
Ahmed and Sayed (13)	Egypt	Cross-sectional study	801	Food addiction scale, Socio-demographic/ anthropometric measurements	The mean scores of food addiction showed a significant increase from overweight to the obese group (23.8% and 43.7%, respectively). The mean scores of food addiction were found to be 32.5%
Siah et al. (14)	Malaysia	Cross-sectional study	333	Food addiction scale, Parental authority questionnaire, Socio-demographic/ anthropometric measurements	No significant relationship was found between food addiction and BMI
Meule et al. (15)	Germany	Experimental study	50	Food addiction scale, Food cravings Questionnaire, Eating disorder examination -questionnaire, Barratt impulsivity scale, Epidemiological studies, Central depression scale, Socio-demographic/ anthropometric measurements	Nineteen out of 50 children with overweight and obesity were reported to be food addicts
Tompkins et al. (16)	United States of America	Experimental study	26	Food addiction scale, Child food power scale, Pediatric quality of life inventory, Socio-demographic/ anthropometric measurements	30.7% of adolescents with obesity met the criteria for food addiction, and 50% ≥3 reported symptoms of food addiction
Borisenkov et al. (23)	Russia	Cross-sectional study	1144	Food addiction scale, Zung self-rating depression scale, Socio-demographic/ anthropometric measurements	Food addiction was found to increase in adolescents with overweight and obesity ($p<0.002$)
Mies et al. (24)	Netherlands	Cross-sectional study	2653	Food addiction scale, Consumption of sugar with beverages, Smoking, drugs and alcohol use behavior, Socio-demographic/ anthropometric measurements	2.6% of the sample was found to be food addicts. The mean scores of food addiction showed a statistically significant increase from thing group to overweight/obese group (1.9%, 2.0%, 5.9%, respectively)
Richmond et al. (25)	United States of America	Cross-sectional study	70	Food addiction scale, Demographic and eating habits questionnaire, anthropometric measurements	Among children, food addiction was more strongly associated with total calories consumed than BMI

Table II. continued

Rodrigue et al. (26)	Canada	Cross-sectional study	969	Food addiction scale, Binge eating scale, Multidimensional anxiety scale for children, Beck depression inventory, UPPS driving behavior scale, Executive functional behavior assessment inventory - self-reporting version, Socio-demographic/ anthropometric measurements	Adolescents with higher food addiction were found to also have a higher BMI
Zhao et al. (27)	China	Cross-sectional study	593	Food addiction scale, Depression epidemiologic center scale, Rosenberg self-esteem scale, UCLA loneliness scale, Problems and challenges questionnaire, Pediatric quality of life inventory, Socio-demographic/ anthropometric measurements	Comparison of adolescents with food addiction to adolescents with no food addiction indicated that the former had a higher BMI (p=0.016)
Filgueiras et al. (29)	Brazil	Cross-sectional study	139	Food addiction scale, Semi-quantitative food frequency questionnaire, Socio-demographic/ anthropometric measurements	95% of overweight children showed at least one of the seven signs of food addiction. In addition, 24% of children with overweight were diagnosed with food addiction.
Laurent and Sibold (32)	United States of America	Quasi-experimental, Cross-sectional study	65	Food addiction scale, Child food power scale, Children's physical activity survey, Dutch eating behavior Questionnaire for children, Depression inventory for children, Multidimensional anxiety scale for children, Socio-demographic/ anthropometric measurements	38% of children were overweight or obese. Addiction-like eating behavior was found in 16% of the children and 4% met the criteria for food addiction
Schulte et al. (33)	United States of America	Cross-sectional study	181	Food addiction scale, Youth eating disorder examination questionnaire, Block food frequency questionnaire, Socio-demographic/ anthropometric measurements	There were significant relationships between food addiction scores and excess weights in adolescents with obesity. A significant correlation was found between food addiction scores and higher consumption of ultra processed foods (calorie, fat, saturated fat, trans fat, carbohydrates, sugar, added sugar)
Şanlier et al. (34)	Turkey	Cross-sectional study	793	Food addiction scale, Body image scale, Beck depression inventory, Socio-demographic/ anthropometric measurements	A positive relationship was found between food addiction and BMI. Mean scores of food addiction showed a statistically significant increase from thin group to overweight/obese group (3.26±1.21, 3.41±1.33, 3.77±1.54, KW test=4,735; 0.05)
Naghashpour et al. (35)	Iran	Cross-sectional study	3908	Food addiction scale, Socio-demographic/ anthropometric measurements	No significant relationship was found between food addiction and BMI
Peters et al. (36)	Germany	Cross-sectional study	228	Food addiction scale, Socio-demographic Anthropometric measurements/leptin measurement	There was a weak relationship between food addiction and leptin in patients with normal weight (ß=-0.11, p=0.022). In contrast, food addiction was significantly associated with higher serum leptin (ß=0.16, p=0.038) in patients with overweight

BMI: Body mass index

According to the homogeneity test results, the Q and I^2 values for food addiction were calculated to be 74,109 and 83.80, respectively.

The squares in the graph show the effect size of the related study, and the lines on both sides of the squares show the upper and lower limits of the effect sizes in the 95% confidence interval (CI). The area of each square shows the weight of the associated study within the overall effect size. The diamond-shaped rhombus at the bottom of the figure shows the overall effect size of the studies (Figure 2).

The effect of food addiction in children on obesity was calculated as a medium effect size according to the random-effects model based on a 95% significance level. When the effect sizes of the studies were examined, the minimum effect size value was determined to be -0.209, and the maximum effect size value was 1.086. At the same time, the effect of food addiction on obesity was found to be significant in 7 studies ($p<0.05$), whereas the effect was not significant in 6 studies ($p>0.05$). When studies with significant effect size were examined [Ahmed and Sayed (13); Burrows et al., (19); Borisenkov et al., (23); Mies et al., (24); Richmond et al., (25); Rodrigue et al., (26); and Zhao et al., (27)], the effect of food addiction on obesity was found to be positively moderate and strong ($p<0.05$, Figure 2). On the other hand, studies conducted by Keser et al. (11), Meule et al. (15), Tompkins et al. (16), Filgueiras et al. (33), Naghashpour et al. (35), and Siah et al. (14) indicated that the effect size relating to the effect of food addiction on obesity was insignificant and that the eating habits of children did not significantly affect their obesity status ($p>0.05$, Figure 2). The overall effect size value of all studies was determined to be 0.346 (95% CI, SE: standard error=0.099) in a confidence interval of 0.152 to 0.539 using the random-effects model. According to the random-effects model, when the mean effect sizes in the 95% confidence interval were examined, food addiction was determined to have a positive and moderate effect on obesity, and food addiction was found to have a significant effect on the obesity status of the child ($p<0.05$, Figure 2).

For testing the publication bias, the study employed Funnel plot, Egger regression, Duval and Tweedie, Rosenthal and Orwin's fail-safe N, and Begg and Mazumdar's rank correlations. In the study, to have a 0-effect size concerning food addiction in children, 274 studies were needed according to the Rosenthal error protection coefficient, 84 studies according to Orwin's error protection coefficient, and 1 study according to Duval and Tweedie's method. According to Begg and Mazumdar and Egger regression analysis ($p>0.05$), there was no publication bias. Also, the existence of publication bias was examined with the help of the Funnel Plot, which is given in Figure 3.

In cases of publication bias in the funnel graph, the effect sizes will appear asymmetrically. In the absence of publication bias, they will show a symmetrical distribution. As is shown in Figure 3, the effect sizes can be said to be in a symmetrical structure. This is one of the cases that show the publication bias is low. As a result of this analysis, it can be said that there may be low publication bias in the study.

Discussion

The need to understand food addiction, which is thought to be one of the factors affecting the increasing obesity in children, has increased in recent years. Moreover, differences in results of various studies make it difficult to reach a clear conclusion on this subject. Therefore, this meta-analysis study aimed to obtain outcomes with a high level of evidence by taking contradictory situations as a starting point. The meta-analysis conducted in the present study found some evidence showing significant moderate and strong effects of food addiction on obesity.

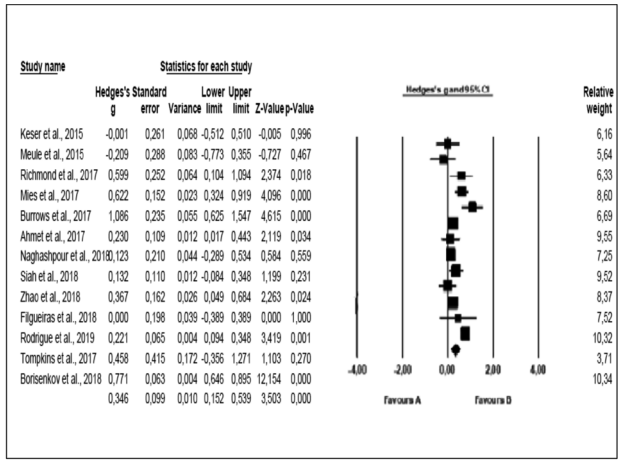

Figure 2. The effect size value of the studies investigating the effect of food addiction in children on obesity

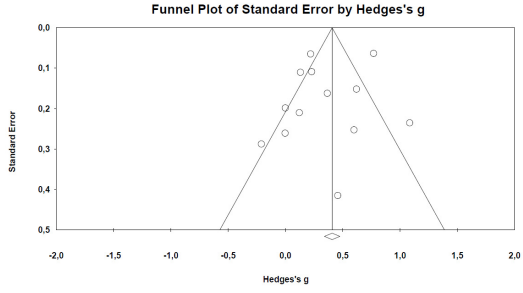

Figure 3. Funnel plot of the effect sizes

Q, p and I^2 values were used in the heterogeneity test of those studies included in this meta-analysis. The Q-value was found to be 74,109, and the I^2 value was around 83.80. In this study, the effect of food addiction in children on obesity was found to be heterogeneous because the Q value was greater than the table X^2 value and the I^2 value was above 75% (31). According to the results of the homogeneity analysis, it was determined that the studies had a heterogeneous structure and that the random effects model should be used. According to sensitivity analyses, when the random effects-model was employed, the results were determined to be similar and the sensitivity was high.

In this study, a total of 17 studies were examined to determine the effect of food addiction in children on obesity. The analyses were conducted with 13 studies that met the inclusion criteria. The sample size of these studies was 10,936. The effect sizes of each study were calculated. In seven studies, food addiction was found to affect obesity, whereas in six studies no significant effect size was found. When the effect sizes of the studies were examined, the minimum effect size value was determined to be -0.209, and the maximum was 1.086. As a result of the analysis of the studies, food addiction was observed to have a moderate to strong effect size on obesity (12,13,23-27), and the effect size was determined to be statistically significant ($p<0.05$, Figure 2). According to the random-effects model, when the overall effect sizes of all of the studies were examined, food addiction was observed to have a positive and moderate effect on obesity, and food addiction was found to significantly affect the obesity status of the child ($p<0.05$, Figure 2). Since there were no meta-analysis studies to determine the effect of food addiction in children on obesity, a comparison of the findings of this first study was not applicable.

While some studies in the literature found that food addiction affected obesity in children (12,13,23,24,26,27,29,32-34), some studies reported that there was no significant effect (11,14-16,35,36). This meta-analysis study revealed that food addiction had an important role on obesity. In this meta-analysis study, particularly, the sub-dimensions of food addiction were thought to have led to obesity in children. These sub-dimensions included children's desire and cravings for some foods and drinks in spite of feeling full; not being able to prevent themselves from eating certain foods; eating more than needed; feeling guilty while consuming certain foods but after a while finding themselves consuming these same foods; unsuccessful attempts to reduce or stop eating; concealing the fact that they consume unhealthy food; frequently making excuses about why they should consume some foods; and failure in controlling the consumption of certain foods despite knowing that they are harmful to health (12,13,23-25).

For testing the publication bias, the study used Rosenthal and Orwin's error protection coefficient, funnel plot, Duval and Tweedie's method, rank correlation, Egger regression, and Begg and Mazumdar's rank correlations. These analyses calculate the number of studies that may be missing in a meta-analysis (14,31). It is recommended to not use a single method in the determination of the publication bias, on the contrary, a set of methods should be considered. When the Rosenthal error protection coefficient, which is one of the technical methods, was examined, the number of studies required to bring the effect size to zero was found to be large, and this indicated that there was no publication bias in this study. However, when other methods were employed in this study, the majority of the methods revealed that the present study might include publication bias. When examining the results of this meta-analysis, this finding should be taken into consideration.

Conclusion

This study provides important findings to determine the effect of food addiction in children on obesity. According to the results of this study, when the average effect size of all studies was examined according to the random-effects model, food addiction was found to have a positive and moderate effect size on obesity, and also, it was determined to have a significant effect on the obesity status of the child ($p<0.05$). In conclusion, food addiction was determined to affect obesity in children. However, the limitation of this study was that the age and gender-related results could not be presented because age and gender-based sub-analyses were not adequate in the studies that were included in the systematic review and meta-analysis. The results of this study are thought to contribute to the knowledge of policymakers and managers so that they can understand the healthy eating behaviour of children and develop strategies for keeping a healthy weight. This study is also expected to provide researchers with a new perspective for future studies. The small number of studies included in this meta-analysis study led to a publication bias; therefore, new studies with a high level of evidence are needed to reveal the effect of food addiction on obesity so that the results can be clarified. In particular, conducting randomized controlled experimental studies and the presentation of effect sizes and power analyses are recommended. In this study, studies employing the same scale were used to maintain objectivity and to prevent bias; for this reason, future meta-analysis

studies are recommended to include studies with other measurement tools.

Ethics

Ethics Committee Approval: The study was approved by the Dokuz Eylül University, Non-Interventional Research Ethics Committee (IRB: 2019/20-14).

Informed Consent: This is a meta-analysis study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Design: M.B., D.D., Ş.D., İ.B., Data Collection or Processing: M.B., D.D., Ş.D., İ.B., Analysis or Interpretation: M.B., D.D., Ş.D., İ.B., Literature Search: M.B., D.D., Ş.D., İ.B., Writing: M.B., D.D., Ş.D., İ.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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J Pediatr Res 2021;8(4):424-31
DOI: 10.4274/jpr.galenos.2021.57689

Original Article

Determining the Knowledge Level of Parents Relating to Circumcision

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ABSTRACT

Aim: This study was conducted to determine the knowledge level and opinions of parents regarding circumcision.

Materials and Methods: This descriptive style study was conducted with 258 individuals who were the parents of male patients being treated in the pediatric surgery department of a university hospital. The data of the study were collected through a questionnaire which was designed in line with the literature and given through a face-to-face interviewing method. The data were analyzed by using descriptive statistics with the SPSS 21.0 package program for Windows.

Results: A total of 84.9% of the parents were the mothers of the children. A total of 70.2% of the parents stated that they had had their child circumcised by a physician in a hospital setting. Regarding the purpose of circumcision, a total of 27.5% of the parents stated medical and emergency requirements while 25.6% of them stated cultural factors. A total of 23.3% of the parents stated that their children did not want to be circumcised while 57.4% stated that they had made decision to circumcise together with their spouse. A total of 54.3% of the parents mentioned that their children experienced pain after circumcision. It was determined that the parents had a moderate level of knowledge regarding the benefits of circumcision, however, most of them had no idea about the practices of circumcision.

Conclusion: Parents emphasized the cultural and medical factors as being the most important factors in the decision to circumcise their child. Parents have a lack of knowledge of circumcision practice, its benefits, and post-circumcision care. Training with the aim of increasing the knowledge of parents regarding circumcision should be planned. Qualitative and quantitative studies on the subject are recommended to be conducted in different regions and with large populations.

Keywords: Circumcision, parent, level of knowledge

Introduction

Circumcision is one of the oldest and most common surgical procedures around the world (1,2). Some factors such as religion, culture, geographical area, race, and ethnicity affect circumcision rates. Although the frequency of circumcision shows differences regionally, it is carried out in almost every region of the world (3,4). According to the World Health Organization report, it is estimated that almost 30-33% of the men aged 15 and above are circumcised (5). It is a commonly performed practice in some parts of South East Asia, in the Americas, The Philippines, The Middle East, Australia, Israel, South Korea, and regions where there is a high density of Muslim population (3,6,7). The majority of men in Turkey, where most of the population is Muslim, are circumcised (8).

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Received: *12.12.2020* **Accepted:** *28.02.2021*

While circumcision is considered as an expression of cultural identity in certain groups, it is associated with social life, health, and reproductive health in many societies (4). It is accepted as a religious component in Jewish and Muslim societies (2). An average of 25% men around the world are circumcised due to religious, cultural, medical reasons, and family preferences, according to reports (9,10).

Circumcision is considered as being a symbol of the ability to reproduce and of a child entering into manhood. Circumcision is directly related to health in addition to its religious and traditional connection (4,8). However, there is no clarity regarding the ethical aspect of circumcision. In the literature, while it is thought that child circumcision is unethical and against human rights, it is also stated that it is a beneficial intervention which can prevent some diseases (2,11).

It is stated that circumcision which is performed in the phallic period may lead to acute psychological issues in children. Therefore, circumcision is recommended to be performed before the age of three or after the age of six (3,12). Religious beliefs, traditions, human rights, financial issues, and scientific data are important aspects of discussions regarding circumcision (8,13). Regardless of the meaning that is attached to circumcision, necessary consideration must be given to the fact that this practice should be carried out for men of all age groups in the best conditions and with the least risk (8,12).

Since circumcision is an important surgical procedure, it should be performed by an experienced doctor in a hospital operating room environment (10,14). Circumcisions performed outside the hospital environment may lead to more complications. It is stated that complications happen mostly in the early period after circumcision and the frequency of the complications varies between 0.2% and 5% (15). Generally, in eastern societies, circumcisions are performed in environments such as the home or neighborhood health center, which are not suitable for any kind of surgical procedure, and they are carried out by people without any expertise or professional competence (10,15,16). While the complication rate of circumcision performed by trained professionals in developed countries is 5%, it may go up to 95% in developing countries when the circumcision is performed by a traditional circumciser (10).

There are a limited number of studies that investigate the opinions and knowledge of parents on circumcision. To give information about circumcision to the parents and raise their awareness about this frequently applied procedure is very important. This study was conducted to determine the knowledge level and opinions of parents regarding circumcision.

Materials and Methods

Study Design

This study is of a descriptive type. This study was conducted between July 2016 and July 2017 with the parents of boys who were treated in the pediatric surgery wards of a university pediatric hospital. The boys had been previously circumcised or were hospitalized due to an existing circumcision operation. The parents' behaviors, thoughts, and knowledge regarding the circumcision process of their boys were evaluated.

Study Population

The parents of child patients being treated in the pediatric surgery department formed the population of this study. The sample of the study was 258 individuals who were the parents of male patients between the ages of 0 to 18 years. The inclusion criteria for the study were as follows; being the parent of a previously circumcised male child between the age of 0 to 18 years who was being treated in the pediatric surgery department or being the parent of child who was at that time in the pediatric surgery ward due to a circumcision operation, and being the primary care provider of the child and agreeing to participate in the study.

Data Collection and Instruments

The questionnaire used in this study was designed by the researchers in line with the literature (17,18). The data were collected through a face-to-face interview method by two of the researchers. The researchers briefed the parents about the study and informed verbal and written consent was obtained from the parents. A "Personal Information Form" and "Circumcision Information Form" were used as the tools to collect data. The personal information form has two sections. The first section includes questions on the socio-demographic parameters of the parents (gender, age, educational background, occupation and income), and the second section includes questions on their behaviors and opinions regarding the practice of circumcision as well as the method they chose for the circumcision of their child. The Circumcision Information Form includes 23 questions which investigate information regarding the parents' level of knowledge on circumcision and care after circumcision.

Statistical Analysis

The SPSS 21.0 package program for Windows was used to analyze the data. The socio-demographic characteristics of the parents and their knowledge regarding circumcision were evaluated by using descriptive statistical methods (frequency and percentage distribution, mean, standard

deviation, etc.). Parametric tests (t-test, variance analysis, etc.) were used to analyze the relationship between the parents' socio-demographic characteristics and their total knowledge scores by considering the data structure (normal distribution of data, homogeneity of variance, etc.). The results were evaluated with a 95% confidence interval and a significance level of $p<0.05$.

In order to conduct this study, the implementation permit (no: 27344949/478-2549) was obtained from the Scientific Ethics Committee of Ege University, and institutional permission was obtained from the children's hospital. In addition, written and verbal informed consent of the parents was obtained before starting the study.

Results

A total of 84.9% of the participants were mothers. Parents who were aged 35 years or above comprised 46.1%. A total of 48.8% of the parents had only primary school graduation and 58.5% of them were housewives. A total of 55.0% of the parents stated that their income is equal to their expenses (Table I).

The results regarding the behaviors of parents related to circumcision are presented in Table II. This table includes the parents' experience and knowledge in the process of circumcision of their boys. The doctors performed the circumcision of 82.2% of the children and a total of 70.2% of the children were circumcised in a hospital environment. 41.5% of the parents stated that the child was not briefed before the circumcision, and 57.4% of parents stated that they made the circumcision decision as a parent of their children. A total of 25.6% of the parents stated that they had the circumcision of their children done for cultural reasons and 23.6% of them for medical reasons. After circumcision, 64.7% of the parents performed the dressings, and 10.5% kept the foreskin. After circumcision, 54.3% of children experienced pain, and 8.9% of them had complications (Table II).

The distribution of the parents' level of knowledge about circumcision is shown in Table III. The mean total score of knowledge is 11.07±16 (minimum 2; maximum 18). Regarding the benefits of circumcision, 64.0% of the parents gave the answer of "the risk of penile cancer decreases" and 48.1% of them gave the answer of "sexually transmitted diseases are less common". Parents mostly lack knowledge about "No clothes should be worn after circumcision.", "The best period for circumcision is between the ages of 3-6 years", "having a shower immediately after circumcision" and "attaching a baby's diaper". The parents

Table I. Distribution of parents' socio-demographic features (n=258)

Variables	Groups	n	%
Gender	Female	219	84.9
	Male	39	15.1
Age	19 years or below	9	3.5
	20-24 years	19	7.4
	25-29 years	37	14.3
	30-34 years	74	28.7
	35 year or above	119	46.1
Education status	Uneducated	6	2.3
	Primary school	126	48.8
	High school	77	29.8
	Undergraduate	35	13.6
	Graduate	14	5.4
Occupation	Housewife	151	58.5
	Private sector employee	38	14.7
	Self-employed	17	6.6
	Government employee	42	16.3
	Retired	10	3.9
Income status	Income is less than spending	93	36
	Balanced	142	55
	Income is more than spending	23	9

Table II. Distribution of parents' behavior related to circumcision (n=258)

Variables	Groups	n	%
The person who performed the circumcision	Doctor	212	82.2
	Health technician	12	4.6
	Circumciser	34	13.2
Place of circumcision	Hospital	181	70.2
	Health center	13	5.0
	Home	64	24.8
Briefing before circumcision	Yes	151	58.5
	No	107	41.5
The decision on circumcision age	Father	41	15.9
	Mother	24	9.3
	Parental decision	148	57.4
	Health professional	35	13.5
	Family elders	10	3.9
Willingness of children	Yes	60	23.3
	No	198	76.7

Table II. Continued			
Reasons for circumcision			
Cultural reasons	Yes	66	25.6
	No	192	74.4
Medical reasons	Yes	61	23.6
	No	197	76.4
Emergency indication	Yes	10	3.9
	No	248	96.1
Performing the dressing after circumcision	Yes	167	64.7
	No	91	35.3
Observing the presence of post-circumcision pain	Yes	140	54.3
	No	118	45.7
Keeping the foreskin	Yes	27	10.5
	No	231	89.5

gave the answer of "I have no idea" most to the following topics: "Sexually transmitted diseases are less common in circumcised children", "Neonatal circumcision is not applied to children with a small genital or congenital disorder", "Neonatal circumcision is not applied to children who are born small, cannot maintain body temperature, and cannot be fed", and "bleeding after circumcision is common".

The results of the analysis performed for the comparison of the total scores of the parents' knowledge on circumcision according to socio-demographic characteristics are given in Table IV. No significant relationship was found between the socio-demographic characteristics of the parents and their total knowledge scores.

Discussion

Parents' opinions and knowledge-levels regarding circumcision were determined with this study. Circumcision has been a common surgical procedure since ancient times (4,19). This study determined that approximately one-fourth of the parents had their children circumcised due to cultural factors. Sardi and Livingston (20) stated in their study that parents had their children circumcised primarily for cultural and personal expectations and then for health reasons. Similarly, in the study of Rızalar et al. (8), 69.3% of the parents stated religious beliefs as the reason for circumcision while 29.1% of them stated cultural factors. Other studies in the literature also stated that almost all parents had their children circumcised due to religious and cultural reasons (19,21). The results of our study show similarities with the literature. The results reveal once again that cultural factors are an important component of circumcision practice. The proportional differences in the results of the research may be related to the size of the study samples, participants living in different regions, and having different traditional structures. While circumcision is considered a religious component in Muslim and Jewish societies (2), it is associated with medical reasons and health in western societies (7). Waskett (22) stated in his report that circumcision is becoming more and more common around the world, however, it is being preferred for health and medical purposes, more than for the cultural and religious reasons. It is stated in another study that some of parents had their children circumcised because of beliefs related to sexuality and cosmetics (23). Similar to studies in the literature, this study's findings show that almost 25% of the parents had their children circumcised due to medical reasons, while a total of 4% of them were due to emergency medical indications. Our study results are consistent with the literature.

Since circumcision is a surgical procedure, it should be performed by specialists following aseptic techniques (4,16). It was determined in this study that more than half of the parents had their children circumcised by a doctor in a hospital setting. In another similar study, 57.9% of the parents stated that they preferred to have their children circumcised by a doctor in a public hospital (23). According to the study of Koç et al. (24), 63.5% of the families had their children circumcised in a hospital setting. Although literature information and study results show that the vast majority of families have their children circumcised safely in a hospital setting, there are also reports that in developing countries and eastern communities, circumcision is still performed at home, in neighborhood health centers, and in crowded areas (such as mass circumcision ceremonies). It is also stated in research reports that in developing countries, circumcision continues to be conducted by non-professional people, who are referred to as "circumcisers" (7,22). The families' lack of knowledge on circumcision, their consideration of circumcision as a simple operation, economic factors, family rituals, and the density of health institutions might be considered as the reasons leading to these situations.

Since circumcision is a surgical procedure, the risk of developing complications may increase if it is not performed under suitable conditions (4,25). In this study, parents stated that 10% of the children developed complications (4,25). Similarly, Altunkol et al. (25) mentioned that 8.7% of the patients that were circumcised developed complications either minor or major. Also, Türkan et al. (26) reported in their study that 12.0% of the children had

Table III. Distribution of the parents' level of knowledge about circumcision (n=258)

Statements	Know		Don't know		No idea	
	n	%	n	%	n	%
Urinary tract infections are more common in circumcised children.	138	53.5	34	13.2	86	33.3
Circumcision leads to better penile cleansing and the rate of penile cancer in children with circumcision decreases.	165	64.0	7	2.7	86	33.3
Sexually transmitted diseases are less common in circumcised children.	124	48.1	10	3.9	124	48.1
Circumcision is used as a treatment for conditions such as tightness in the foreskin, bonded foreskin, and paraphimosis.	199	77.1	12	4.7	47	18.2
In our country, males must be circumcised to get married.	207	65.9	46	17.8	42	16.3
Circumcision may lead to emotional stress in children.	170	65.9	46	17.8	42	16.3
No clothes should be worn after circumcision.	90	34.9	117	45.3	51	19.8
Neonatal circumcision is not applied to children with small genitals or a congenital disorder.	65	25.2	27	10.5	166	64.3
Neonatal circumcision is not applied to children who are born small, cannot maintain body temperature, or cannot be fed.	52	20.2	41	15.9	165	64.0
The child who is entering the adolescence period cannot be circumcised.	99	38.4	71	27.5	88	34.1
Children with hemophilia should not be circumcised without taking the necessary precautions.	193	74.8	19	7.4	46	17.8
Complications will develop after circumcision if the aseptic conditions are not maintained.	170	65.9	26	10.1	62	24.0
The younger the child is, the more difficult the circumcision is.	119	46.1	69	26.7	70	27.1
The most common thing after circumcision is bleeding.	105	40.7	43	16.7	110	42.6
Circumcision should not be performed in the neonatal period.	118	45.7	67	26.0	73	28.3
The best period for circumcision is between the age of 3-6 years.	76	29.5	102	39.5	80	31.0
The child can ride a bicycle the day after circumcision.	222	86.0	14	5.5	22	8.5
The child can take a shower immediately after circumcision.	26	10.1	181	70.2	51	19.8
Having a shower every day after circumcision speeds up the recovery.	38	14.7	121	46.9	99	38.4
If the baby is using a diaper, it should not be changed frequently.	117	45.3	98	38.0	43	16.7
If the baby is using a diaper, it should be attached loosely.	20	7.8	198	76.7	40	15.5
Straining leads to increased bleeding and constipation in circumcised children.	87	33.7	37	14.3	134	51.9
Since the sense of pain does not develop in the newborn, circumcision can be performed without anesthesia.	41	15.9	80	31.0	137	53.1

complications developing after circumcision. The results of this study show similarities with the complication rates in the literature. Performing circumcision in settings not suitable for surgical procedures, circumcision being performed by non-professionals, and the parents' lack of knowledge on post-circumcision care might be the leading factors for the development of complications. Moreover, it is widely believed that hastily performing circumcision when performed in a mass environment might lead to the development of complications as well as infections.

Although circumcision is considered to be a sociological need, it is a topic of discussion on medical ethics and patient rights due to its possible psychological effects on male children. Especially, there are different opinions on the appropriate age for circumcision (27,28). The findings of our study determined that almost two-thirds of the children were not willing to be circumcised, while more than half of the parents stated that they decided on the circumcision. Similar studies in the literature mention that parents decide on circumcision (24,29). According to the results of this study, although parents have the biggest determining element on circumcision, briefing the child about circumcision and getting his opinion should be considered in terms of personal rights and ethics.

Table IV. Comparison of parents' total scores on circumcision knowledge levels by socio-demographic characteristics

Variables	Groups	n	X ± SD	Statistical value
Gender	Female Male	219 39	43.76±6.81 43.79±6.74	t: 0.02* p: 0.98*
Age	19 year or below	9	40.66±6.02	F: 0.57** p: 0.68
	20-24 years	19	43.94±6.84	
	25-29 years	37	44.13±5.21	
	30-34 years	74	43.48±6.05	
	35 year or above	119	44.04±7.67	
Education status	Uneducated	6	42.66±5.53	F: 1.67** p: 0.15
	Primary school	126	44.34±6.88	
	High school	77	42.17±1.21	
	Undergraduate	35	40.50±7.06	
	Graduate	14	43.77±6.78	
Occupation	Housewife	151	43.77±6.49	F: 1.61** p: 0.17
	Private sector employee	38	45.55±7.84	
	Self employed	17	42.11±6.78	
	Government employee	42	42.33±6.78	
	Retired	10	45.80±2.97	
Income status	Income is less than spending	93	45.52±6.97	F: 1.80** p: 0.16
	Balanced	142	43.10±6.43	
	Income is more than spending	23	44.35±7.19	
The person who performed the circumcision	Doctor	212	43.75±6.76	F: 1.47** p: 0.86
	Health technician	12	42.91±6.81	
	Circumciser	34	44.14±7.11	

*t- test, **ANOVA
SD: Standard deviation

Circumcision might be a painful, traumatic experience that is perceived as emotionally negative (29,30). There are a few studies about the prolonged psychological effects of male circumcision. Goldman (31) stated in their study that circumcised males generally experience feelings of anger, embarrassment, grief, instability, and of being abused. Therefore, circumcision is recommended to be performed at the ages when the psychological effects are minimal and by a doctor (28). It was determined in this study that parents do not have sufficient knowledge of the appropriate age for circumcision. Similarly, in other studies in the literature, parents did not know much about the appropriate age levels for circumcision (24,29,32). These studies mostly state that children are circumcised at school age. Özkan et al. (33) stated in their study that 44.8% of circumcisions were conducted while the children were in the phallic period. Circumcision is a condition that significantly affects a child's inner world and sense of self. Therefore, when determining the age of circumcision, the psychological effect of the circumcision on the child should be taken into consideration, and children's emotional reactions and their perceptions should be evaluated (15). Especially, circumcision that is conducted between the ages of 3 to 6 years might lead to a negative experience for the children as, during this period, the children's sexual identity begins to develop and their genitals start to have meaning and value from the child's point of view. Especially, they might experience fear of losing their genitals (castration) during this period. Due to these reasons, it is recommended that circumcision is conducted before the age of 3 or after the age of 6 years (27,28). Also, it is thought that families prefer to carry out circumcision during the school-age after children develop concrete perceptions so that their children can remember it as a pleasant ritual.

It was determined that the parents in this study did not have sufficient knowledge regarding the benefits of circumcision. Approximately half of the parents have wrong information regarding the practice of neonatal circumcision. There is scientific evidence on the possible medical benefits of neonatal circumcision. However, this evidence is not sufficient to recommend neonatal circumcision as a routine practice (34). It is stated that neonatal circumcision decreases the risk of urinary tract infections, HIV, and other sexually transmitted diseases and the development of carcinoma in the penis (34,35). In a meta-analysis study in which 1,000 circumcised adults in Africa were examined, it was reported that circumcision reduces the risk of HIV by 38-64% (11). A low level of education among the parents and the fear of newborns being harmed might affect the knowledge level of the parents regarding neonatal circumcision. Besides, the parents' lack of knowledge on a child's development periods as well as not knowing about sexual identity acquisition of the child in the phallic period may cause them to have difficulties with the decision of circumcision age.

Correctly applied post-circumcision care is effective in reducing the risk of complications after circumcision (36). According to the results of this study, parents have a moderate level of knowledge of post-circumcision care and procedures. In contrast to our results, a study conducted

with mothers revealed that the knowledge level of the mothers on post-circumcision care and complications was above average (21). It was reported in studies investigating the post-circumcision status that bleeding, insufficient circumcision, fistula, and infection are the complications observed frequently (16,33). These results reveal the necessity of following aseptic techniques for care both during the circumcision procedure and in the post-circumcision period. It is thought that it is necessary to provide education on post-circumcision care to mothers, as they are often the primary caretakers, in order to manage successful post-circumcision care and reduce the risk of infection.

Study Limitations

This study had some limitations. This study was conducted with the parents of male patients being treated in the pediatric surgery department of a university hospital. The data was limited to the level of knowledge of parents regarding circumcision and provided information about the current situation. During data collection, 20 participants did not want to complete the study, and therefore, their data were excluded from the study. The targeted number of samples was reached in the general framework and a reliable and high rate of response was received from the participants. Applying valid and reliable assessment tools which are used to measure the knowledge of individuals regarding circumcision in the study could contribute to a clearer demonstration of the effectiveness of the results.

Conclusion

Circumcision is a process that includes religious, traditional, and medical dimensions. In addition, this process has an important effect on a child's psychology and their sense of self. The results of this study revealed that parents do not have sufficient or accurate information on circumcision. Also, a child's opinion is not taken into account when making decisions on circumcision and parents have the final say on these decisions. Due to this, health professionals (doctors, nurses, primary care physicians, etc.) should provide the necessary education to the parents and society on circumcision, and awareness should be increased with educational activities. It is recommended to conduct qualitative and quantitative studies in larger sample groups and in different regions to evaluate families' knowledge and opinions on circumcision. In addition, qualitative studies evaluating the children's perception of circumcision should be conducted in order to take their opinions into consideration.

Acknowledgement

The authors are grateful to acknowledge all participating parents in this study.

Ethics

Ethics Committee Approval: This study was approved by the Ege University Faculty of Nursing, Scientific Ethics Committee of the University (approval number: 27344949/478-2549) and by the clinic where the study was conducted.

Informed Consent: Written informed consent was obtained from the participants before enrollment.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: N.A.D., A.K., H.N.Ç.Ö., Design: N.A.D., A.K., H.N.Ç.Ö., Data Collection or Processing: H.N.Ç.Ö., A.K., Analysis: A.K., Interpretation: A.K., H.N.Ç.Ö., Literature Search: N.A.D., A.K., H.N.Ç.Ö., Writing-review: H.N.Ç.Ö., A.K., Editing, and supervision: N.A.D., A.K., H.N.Ç.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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J Pediatr Res 2021;8(4):432-7
DOI: 10.4274/jpr.galenos.2021.48751

Original Article

A Comparison of Clinical Findings and Laboratory Test Results Between Hospitalized Children with COVID-19 and Influenza

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ABSTRACT

Aim: It can be challenging to distinguish between influenza and coronavirus disease-2019 (COVID-19) during the influenza season. Therefore, we aimed to compare the clinical symptoms, laboratory findings, and outcomes of these two diseases in children.

Materials and Methods: Thirty-two children with COVID-19 and 22 children with influenza who were hospitalized in our clinic were included in this study. The demographic, clinical, and laboratory findings of these patients were retrospectively reviewed.

Results: The median age of patients with influenza and COVID-19 was 1.4 and 15.3 years, respectively. Fever (77.3% vs 46.9%, p=0.02), nasal obstruction (27.3% vs 0%, p=0.003), wheezing (54.5% vs 3.1%, p<0.001), bilateral crackling sounds (63.6% vs 15.6%, p<0.001), prolonged expirium (63.6% vs 3.1%, p<0.001), tachycardia (36.4% vs 0%, p<0.001) and tachypnea (54.5% vs 0%, p<0.001) were significantly more frequent in those patients with influenza compared to COVID-19. Patients with influenza had significantly increased leucocyte count, lymphocyte count, and aminotransferase levels and lower albumin levels compared to those patients with COVID-19. In the influenza group, three patients needed intensive care, and one of them died. None of the patients with COVID-19 needed intensive care and there was no death in this group.

Conclusion: In hospitalized children, the clinical and laboratory findings were milder in those patients with COVID-19 compared to influenza.

Keywords: Children, coronavirus, COVID-19, influenza

Introduction

Influenza viruses and coronaviruses (CoVs) are common pathogens which cause respiratory disease in humans. CoVs cause intestinal and respiratory infections in humans and animals. Until 2019, six types [common CoVs, and severe ones such as severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1) and middle east respiratory syndrome (MERS) CoV] which caused infection in humans were known. In December 2019, a new CoV, SARS-CoV-2, was identified in Wuhan, Hubei province of China (1-3). The disease caused by SARS-CoV-2 was officially named coronavirus disease-2019 (COVID-19) (1,2).

People of all ages have been affected in the global pandemic of COVID-19. Severe respiratory involvement requiring mechanical ventilation is more common in adults.

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Received: *21.01.2021* **Accepted:** *28.02.2021*

Children are also affected by COVID-19, but their symptoms are milder than those of adults (4,5). During the COVID-19 pandemic, children experience symptoms that are observed in other viral infections such as fever, dry cough, rhinorrhea, sore throat, fatigue, diarrhea, and vomiting (1,4). Rarely, dyspnea or hypoxemia have also been described. Since routine blood tests and imaging have little value in viral infections, it is difficult to distinguish these symptoms from other viral diseases.

Influenza A and B viruses cause respiratory infections with cough and fever symptoms and affect many people each year. Symptoms of COVID-19 can be confused with respiratory diseases caused by influenza viruses (6-8).

The current polymerase chain reaction (PCR) tests for influenza and SARS-CoV-2 may be negative in some patients. However, recognizing these diseases at the time of admission to the hospital may enable healthcare professionals to take precautions quickly and determine the type of patient. For this reason, in this study, we aimed to determine any differences between these diseases by comparing the demographic, clinical, and laboratory findings of children with influenza and COVID-19. In the literature, there are a limited number of studies on children regarding this subject.

Materials and Methods

The study was carried out in accordance with the Helsinki Declaration. University of Health Sciences Turkey, İstanbul Haseki Training and Research Hospital Clinical Research Ethics Committee approved the study protocol (date: 08/07/2020, number: 91-2020).

Patients

The study consisted of two patient groups: influenza and COVID-19. The medical records of 22 patients with influenza who were hospitalized in our hospital between January 1st, 2019, and February 1st, 2020, were retrospectively analyzed. Nineteen of these patients were Influenza A, and three were Influenza B. The patients with influenza infection were confirmed by a positive result for real-time reverse transcriptase-PCR (RT-PCR) multiplex via nasopharyngeal swab samples. Thirty-two patients who were hospitalized in our clinic between March 14th, 2020, and April 30th, 2020, were included in the COVID-19 group. The patients with COVID-19 were confirmed by a positive result for real-time RT-PCR via nasopharyngeal swab samples. Patients aged over 18 years were excluded. All patients had routine laboratory tests, including routine blood examination and biochemistry. No patient had had an influenza vaccine.

Sampling and Detection of Influenza and SARS-CoV-2 Viruses

Respiratory specimens were taken via Dacron-tipped swabs within 24 hours of admission. Influenza viruses were detected from nasopharyngeal specimens using RT-PCR multiplex testing (Qiagen, Germany). The kit also detects other human respiratory viral pathogens (human parainfluenza virus 1/2/3/4, respiratory syncytial virus A/B, human metapneumovirus, human CoV 229E/NL63/OC43, rhinovirus A/B/C, enterovirus, adenovirus, and human bocavirus 1/2/3/4) in addition to influenza A and B.

SARS CoV-2 was investigated using RT-PCR (Bioksen ArGe Teknik Co. Ltd, Turkey; Biospeedy®). If the first sample was negative for SARS-CoV-2 RNA at our clinic, a second specimen was sent for repeat-testing 24 hours after the first one. If the first or the second test was positive, the patient was accepted as a positive COVID-19 case.

Data Collection

Data regarding demographics, clinical and laboratory findings, treatments, and complications of the patients were recorded retrospectively from the medical records. The laboratory results of the patients on the day of admission were acquired.

Statistical Analysis

Statistical analysis was performed on SPSS 15.0 software. Numbers and percentages were used to express categorical variables; the median was used for numerical variables. The Mann-Whitney U test was used to compare median values between two groups, depending on the sample distribution. Categorical variables were compared using the chi-square test. $p<0.05$ was regarded as the alpha (α) significance level.

Results

The median age of those patients with influenza and COVID-19 was 1.4 and 15.3 years, respectively, which was significantly higher in the COVID-19 group. The COVID-19 group was comprised of 53.1% males (n=17), whereas the influenza group was comprised of 77.3% males (n=17), however this difference was not significant. Seven patients (31.8%) had underlying comorbidities in the influenza group, namely, four neurological, two cardiac, and one renal disease. Only two patients had comorbidity (6.2%) in the COVID-19 group, namely, one neurological and one renal disease. However, no significant difference was found between the two groups according to comorbidities (Table I).

At the time of admission, the mean duration of symptoms was three days (range: 1-8) in the influenza group and two days (range: 0-14) in the COVID-19 group, which was not statistically significant. Fever (77.3% vs 46.9%, p=0.02), nasal obstruction (27.3% vs 0%, p=0.003), and wheezing (54.5% vs 3.1%, p<0.001) were statistically more frequent in the influenza group than in the COVID-19 group. As for the findings of physical examinations, bilateral crackling sounds (63.6% vs 15.6%, p<0.001), prolonged expirium (63.6% vs 3.1%, p<0.001), tachycardia (36.4% vs 0%, p<0.001) and tachypnea (54.5% vs 0%, p<0.001) were also significantly more frequent in the influenza group than in the COVID-19 group (Table I).

Bronchodilator therapy, inhaled steroids and IV steroids were used at a higher rate in the influenza group than in the COVID-19 group. Those patients with influenza were hospitalized for a mean duration of 9 days (range: 4-28). During hospitalization, eight patients (36.4%) required nasal oxygen therapy and four patients (18.2%) needed high flow oxygen (HFO) therapy in the influenza group. Concerning the outcome, in the influenza group, three patients were admitted to the Pediatric Intensive Care Unit (PICU) for acute respiratory failure, and one of them died. No patient with COVID-19 required admission to the PICU (Table II).

A comparison of the blood tests showed that leucocyte count and lymphocyte count were significantly lower in those children with COVID-19 (5.5 vs 8.7x10^3/mm^3, p=0.02; 1.8 vs 2.7x10^3/mm^3, p=0.01, respectively) while hemoglobin and albumin were significantly lower in the influenza group (10.6 vs 13.3 g/dL, p<0.001; 39 vs 43 g/L, p<0.001).

Table I. Demographic and clinical characteristics of patients with COVID-19 and influenza infection

Variables	**Influenza (n=22)**	**COVID-19 (n=32)**	**p-value***
Age, years	1.4 (0.5;3.0) range: 0.2-4.5	15.3 (11.5;17.0) range: 0.1-17.1	**<0.001**
Male, n (%)	17 (77.3)	17 (53.1)	0.07
Days of symptoms	3 (1;7), (range: 1-8)	2 (1;3) (range: 0-14)	0.30
Fever, n (%)	17 (77.3)	15 (46.9)	**0.02**
Headache, n (%)	0	6 (18.7)	0.07
Myalgia, n (%)	1 (4.5)	1 (3.1)	1.0
Fatique, n (%)	0	2 (6.3)	0.5
Backache, n (%)	0	3 (9.4)	0.26
Artralgia, n (%)	0	1 (3.1)	1.0
Nazal obstruction, n (%)	6 (27.3)	0	**0.003**
Cough, n (%)	19 (86.4)	22 (68.8)	0.13
Wheezing, n (%)	12 (54.5)	1 (3.1)	**<0.001**
Shortness of breath, n (%)	10 (45.5)	8 (25)	0.12
Vomiting, n (%)	2 (9.1)	7 (21.9)	0.28
Diarrhea, n (%)	2 (9.1)	4 (12.5)	1.0
Abdominal pain, n (%)	0	2 (6.3)	0.5
Co-morbidity			0.07
Neurological	4 (18.2)	1 (3.1) 1 (3.1)	
Renal	1 (4.5)		
Congenital heart disease	2 (9.1)		
Crepitation, n (%)	14 (63.6)	5 (15.6)	**<0.001**
Prolonged expiration, n (%)	14 (63.6)	1 (3.1)	**<0.001**
Tachycardia, n (%)	8 (36.4)	0	**<0.001**
Tachypnea, n (%)	12 (54.5)	0	**<0.001**

*Mann-Whitney U test was performed for continuous data and $\chi 2$ testing was performed for the categorical data. Data are given as median (25^{th};75^{th} percentile) or n (%)
COVID-19: Coronavirus disease-2019

Table II. Treatment and outcome in patients with COVID-19 and influenza infection

Variables	Influenza (n=22)	COVID-19 (n=32)	p-value*
Antibiotic treatment, n (%)	20 (90.9)	32 (100)	0.16
Inhaler steroids, n (%)	9 (40.9)	1 (3.1)	**0.001**
IV steroids, n (%)	10 (45.5)	0	**<0.001**
Bronchodilators, n (%)	15 (68.2)	1 (3.1)	**<0.001**
Antiviral treatment, n (%)	15 (68.2)	20 (62.5)	0.23
Inotropic treatment, n (%)	1 (4.5)	0	0.40
Nasal O^2 treatment, n (%)	8 (36.4)	2 (6.3)	**0.01**
HFO, n (%)	4 (18.2)	0	**0.02**
Days of hospitalization	9 (7;11), range: 4-28	8 (6;9), range: 2-14	**0.04**
Outcome			**0.04**
PICU, n (%)	3 (13.6)	0	
Excitus, n (%)	1 (4.5)	0	

*Mann-Whitney U test was performed for continuous data and $\chi 2$ testing was performed for the categorical data. Data are given as median (25^{th};75^{th} percentile) or n (%)
COVID-19: Coronavirus disease-2019, HFO: High flow oxygen, PICU: Pediatric Intensive Care Unit

The median aspartate aminotransferase (AST) level was significantly higher in the influenza group than in the COVID-19 group (52 vs 24 IU/L, p<0.001). Urea and creatinine levels were significantly higher in those patients with COVID-19 than the influenza patients (17.9 vs 22.9 mg/dL, p=0.02; 0.26 vs 0.56 mg/dL p<0.001, respectively). The other markers had no significant difference between the two groups (Table III).

Discussion

In this study, we aimed to investigate the similarities and differences between COVID-19 and influenza in children. The differentiation between COVID-19 and influenza may be difficult in clinical practice, especially during the COVID-19 outbreak.

SARS-CoV-2 and influenza virus are transmitted similarly by respiratory droplets. In a study conducted in Hong Kong in January, the effects of interventions taken against COVID-19, such as social isolation, distancing, wearing masks, school closures, etc. on influenza transmission were investigated. As a result, the measures were shown to reduce influenza transmission as well as COVID-19 transmission significantly. That study showed that common factors are effective in the transmission of both diseases (9). Another study showed a decrease in influenza cases in China, Italy, and US, where the COVID-19 pandemic was seen as common and early. That result is attributed to the precautions taken against COVID-19 (10).

Unlike influenza, in children, the symptoms of COVID-19 are milder than in adults, and many children are asymptomatic (4). In our study, the most common symptoms in the COVID-19 group were fever, cough, vomiting, and headache, as in the medical literature (4). In a study by Qiu et

Table III. Laboratory findings of patients with COVID-19 and influenza infection

Variables	Influenza (n=22)	COVID-19 (n=32)	p-value*
Leucocytes, $\times 10^9$/L	8.7 (5.6;12.2)	5.5 (4.4;8.8)	**0.02**
Neutrophils, $\times 10^9$/L	4.2 (2.0;6.9)	2.9 (1.9;4.0)	0.19
Lymphocytes, $\times 10^9$/L	2.7 (1.5;4.5)	1.8 (1.3;2.3)	**0.01**
Hemoglobin, g/dL	10.6±1.6	13.3±1.5	**<0.001**
Platelets, $\times 10^9$/L	241 (130;381)	218 (195;262)	0.84
MPV, fL	9.9±1.06	10.2±0.90	0.17
PDW, fL	11.3 (10.2;12.4)	11.4 (10.1;13.0)	0.81
CRP, mg/L	8.9 (4.9;43.8)	3.8 (1.2;23.0)	0.12
Neutrophil/ lymphocyte	1.24 (0.42;1.89)	1.55 (1.01;2.43)	0.28
Platelet/ lymphocyte	78.7 (46.3;99.5)	124 (89.1;163)	**0.001**
SII	226 (119;599)	317 (212;621)	0.17
Albumin, g/L	39±4.3	43±2.6	**<0.001**
Urea, mg/dL	17.9 (12.1;23.2)	22.9 (17.9;26.6)	**0.02**
Creatinine, mg/L	0.26 (0.21;0.31)	0.56 (0.45;0.64)	**<0.001**
Uric acid, mg/dL	3.2 (2.5;4.5)	4.2 (3.5;5.0)	0.04
Sodium, mmol/L	138±4.4	137±3.3	0.74
Potassium, mmol/L	4.4±0.80	4.2±0.44	0.11
Chloride, mmol/L	105±4.5	103±3.2	0.08
Ca, mg/dL	8.8±2.2	9.5±0.42	0.18
AST, IU/L	52 (40;81)	24 (21;35)	**<0.001**
ALT, IU/L	21 (14;30)	14 (13;21)	0.054
Ph	7.38±0.06	7.39±0.06	0.69
pCO^2, mmHg	37±6.6	42.6±8.2	0.06
HCO^3, mmol/L	22.8±4.1	24.0±2.0	0.34

*Mann-Whitney U test was performed for continuous data. Data are given as mean ± standard deviation, median (25^{th}-75^{th} percentile)
COVID-19: Coronavirus disease-2019, MPV: Mean platelet volume, PDW: Platelet distribution width, CRP: C-reactive protein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

al. (11), the most common symptoms were fever (36%) and dry cough. Other symptoms were sore throat, pharyngeal congestion, dyspnea or tachypnea, vomiting, and diarrhea (11). In our study, cough and fever were the two most common clinical symptoms of the influenza and COVID-19 groups. Headache was also a common symptom in children with COVID-19. Nasal obstruction was observed significantly more frequently in the influenza group than in the COVID-19 group. A study conducted in Wuhan reported that nasal obstruction was a common symptom in patients with both influenza and SARS-CoV-2 infection, but not common in patients with only SARS-CoV-2 infection (12). However, it was noted that the presence of this symptom alone would not be sufficient to rule out the possibility of COVID-19 (12). In a recent international study, the most common findings in children with influenza and COVID-19 were fever and cough (13). In that study, dyspnea, bronchiolitis, anosmia, and gastrointestinal system findings were observed more frequently in those children and adolescents with COVID-19 than in children with influenza. The authors reported that their findings are essential in distinguishing COVID-19 from influenza in children (13).

In a large-scale study from the US, children with COVID-19 and influenza did not differ in rates of hospitalization, PICU admission, or mechanical ventilator support (14). These results are not compatible with our study. In our study, the duration of hospitalization, PICU admission rates, requirements of nasal oxygen, and HFO support for those children with influenza were higher than for COVID-19 patients. However, in the aforementioned study, the median age of the patients with influenza was higher, in addition the number of patients with comorbidity was higher in the COVID-19 group when compared to our study.

In Zayed et al.'s (15) study, crackling sounds were statistically more frequent in an adult COVID-19 group than in an influenza group. In contrast to that study, we found that pulmonary auscultation findings were significantly more frequent in children with influenza. This difference may be attributed to the fact that involvement of the lungs is more common and the disease course is more severe in adult COVID-19 cases compared to children.

In our study, a higher rate of lymphopenia was observed in children with COVID-19. Lymphopenia is common in patients with COVID-19. We found leukocytosis, hypoalbuminemia, and elevated AST levels in children with influenza. These results were attributed to the more severe clinical course of the influenza group. In a study conducted in China, AST was found to be higher in children with influenza than in those with COVID-19 (16).

Li et al. (2) compared COVID-19 and influenza A patients under five years of age who had been hospitalized for pneumonia. They showed that the clinical course of COVID-19 patients was milder than that of influenza A patients (2). Similar to the results of their study, we observed that the clinical findings and prognosis for children with COVID-19 were milder than for children with influenza.

During the influenza season, influenza and COVID-19 co-infections have been reported in adults (6,17-19). This co-existence indicates the importance of investigating SARS-COV-2 in patients with respiratory findings even if the influenza virus has been detected. SARS-COV-2 RT-PCR can give false negative results. Therefore, suspicious cases need to be tested several times. Wu et al. (19) reported a senior case with COVID-19 and influenza A. After four negative nasopharyngeal swab specimens for SARS-CoV-2, the fifth sample taken from bronchoalveolar lavage fluid was found to be positive for SARS-CoV-2. In the beginning, when the patient's influenza A test was positive, his symptoms were attributed to influenza, and he was discharged to home. The patient was hospitalized again a few days later with signs of severe respiratory failure. False negative RT-PCR results make diagnoses rather challenging in the influenza season. However, the co-infection of these two infections must not be missed. In one study from Wuhan in China, throat swabs of 640 patients with influenza-like illnesses, of whom 142 were positive for an influenza test, from October 6th, 2019, to January 21st, 2020, were retrospectively investigated, and nine of these patients were found to be positive for COVID-19 (3).

Study Limitations

The first limitation of our study was the small sample size. Secondly, in our study, other viral agents could not be studied in the COVID-19 group as virology laboratories stopped other tests to focus on COVID-19 testing. An influenza antigen test was performed on eleven patients with COVID-19 and was found to be negative in all of them. In the months when the study was conducted, influenza was not common in our country.

Conclusion

In our study, children with COVID-19 had a milder clinical course than those with influenza. This result can be attributed to two factors; first, the median age was lower in our group of children with influenza. Influenza shows higher morbidity and mortality in younger ages. Second, the

children with COVID-19 had less comorbidity. Comorbidity of patients with COVID-19 leads to a worse prognosis. COVID-19 and influenza show similar symptoms in children. The role of symptoms in differentiating between these two diseases is rather limited.

Ethics

Ethics Committee Approval: Health Sciences Turkey, İstanbul Haseki Training and Research Hospital Clinical Research Ethics Committee approved the study protocol (date: 08/07/2020, number: 91-2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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J Pediatr Res 2021;8(4):438-43
DOI: 10.4274/jpr.galenos.2021.09851

Original Article

The Status of Vitamin D Among Children Aged 0 to 18 Years

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ABSTRACT

Aim: This study aimed to examine the status of vitamin D in children, to compare vitamin D levels according to the seasons, and to estimate vitamin D testing trends during the years of the study.

Materials and Methods: Blood 25-hydroxyvitamin D [25(OH)D] levels of 51,560 children aged between 0-18 years who had been admitted to nine hospitals between 2015 and 2017 were evaluated. Comparisons of 25(OH)D levels with age groups, gender, and seasons were made. Additionally, vitamin D testing was compared year by year in terms of frequency.

Results: Of the patients, 20% (n=10,611) had vitamin D deficiency and 34% (n=17,385) had vitamin D insufficiency. Serum 25(OH)D levels were significantly higher in boys than in girls ($p<0.01$). There was a significant difference between serum 25(OH)D levels and the age groups. The highest mean 25(OH)D levels were detected in infants (33.95 ng/mL) and the lowest in adolescents (18.3 ng/mL). Significant seasonal variability of 25(OH)D levels was detected ($p<0.01$). Vitamin D deficiency was determined most frequently in winter with a frequency of 30.7%. A three-fold increase in 25(OH)D testing was determined over the 3-year period.

Conclusion: Female gender, adolescence, and the winter season were found to be important risk factors for vitamin D deficiency or insufficiency. Further evidence is needed to clarify whom to test in order to avoid over-testing.

Keywords: Children, 25-hydroxyvitamin D, seasonality, vitamin D deficiency

Introduction

The main source (about 90%) of vitamin D is synthesized in the skin from provitamin D3 (7-dehydrocholesterol) upon ultraviolet B exposure and 10% comes from animal-derived foods with oily fish being the most important (1). Vitamin D plays a key role in regulating calcium and phosphorus homeostasis and bone health. Vitamin D also exerts extra-skeletal actions. A growing number of studies have demonstrated that low vitamin D status plays a possible role in the pathogenesis of several pathological conditions, including infectious, allergic, neuropsychiatric, and autoimmune diseases (2).

It is widely acknowledged that 25-hydroxyvitamin D [25(OH)D] serum concentration is the best indicator to evaluate vitamin D status. In the literature, several cut-off points have been proposed for vitamin D levels (2). A global consensus statement of 11 international scientific societies defined 25(OH)D levels as follows; >50 nmol/L

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Received: *11.12.2020* **Accepted:** *18.03.2021*

(>20 ng/mL) indicates sufficiency, 30-50 nmol/L (12-20 ng/mL) indicates insufficiency and <30 nmol/L (<12 ng/mL) indicates deficiency (3). Vitamin D insufficiency and deficiency are common worldwide among children of all age groups (4-6).

The winter season, non-white ethnicity, the amount of time spent outdoors during summer, female gender, higher age, higher Tanner stage, and lower household income have all been observed to be associated with vitamin D deficiency in childhood (7). The dietary vitamin D intake is often insufficient to cope with the seasonal deficits of sunlight exposures during winter. Vitamin D deficiency is an important problem in countries with relatively low sun exposure (1). Seasonal variability of 25(OH)D concentrations in children has been reported in studies from different countries (4-6).

Most patients with vitamin D deficiency are asymptomatic, so whom to test is becoming a major question. Also, increasing awareness of vitamin D deficiency among physicians, the media, and the public causes vitamin D to be more or over investigated in comparison with previous years (8). Reports demonstrate that there is over-screening, overdiagnosis, and overtreatment for vitamin D deficiency in healthy individuals (9). Large increases in vitamin D testing have been reported from Australia, the UK, and the USA in recent years (9-11). A similar increase has been observed in our country, Turkey, but there has been no study on this subject to date. This study aimed to examine vitamin D status in children aged between 0 and 18 years, to compare vitamin D levels according to the seasons, and to evaluate vitamin D testing trends during the years of our study.

Materials and Methods

In this study, the data of 51,560 children aged between 0 and 18 years who had been admitted to nine hospitals in Ankara between the years 2015 and 2017 were evaluated. The hospitals participating in the study were Ankara Dr. Sami Ulus Maternity and Children's Health and Diseases Training and Research Hospital, Ankara Children's Hematology-Oncology Training and Research Hospital, Ankara Numune Training and Research Hospital, Ankara Yüksek İhtisas Training and Research Hospital, Dr. Zekai Tahir Burak Women's Health Education and Research Hospital, Ankara Physical Medicine and Rehabilitation Training and Research Hospital, Haymana State Hospital, Şereflikoçhisar State Hospital, and Ankara Gölbaşı Şehit Ahmet Özsoy State Hospital. The present study was approved by the Ethics Committee of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (15.05.2019/297). Informed consent was not obtained because this was a retrospective study.

The data regarding blood 25(OH)D levels were obtained from hospital registration systems and recorded on a chart. The children were categorized into age groups as follows; infancy group (0-2 years), preschool age group (3-5 years), school-age group (6-9 years), and adolescents (10-18 years). 25(OH)D level determination had been made by tandem mass spectrometry (LC-MS/MS) using API 3200 (Applied Biosystem Sciex, Concord, Canada, L4K4V8) from blood samples where 25(OH)D levels were determined in units of "ng/mL". Vitamin D levels were classified into three groups as follows; <12 ng/mL indicating deficiency, 12-20 ng/mL indicating insufficiency, and >20 ng/mL indicating normal (3). The seasonal variation of serum 25(OH)D levels was also evaluated. The seasons were categorized as "Spring" (March-April-May), "Summer" (June-July-August), "Autumn" (September-October-November), and "Winter" (December-January-February). Comparisons of 25(OH)D levels with age, gender, and the seasons were made. Vitamin D testing was compared year by year in terms of frequency.

Statistical Analysis

Statistical analysis of the data was performed using the SPSS 20.0 software system for Windows (IBM Corp., Armonk, NY). Frequency and percentage values were given for nominal variables and mean and standard deviation values for continuous variables. Student's t-test was used to investigate the difference in vitamin D levels between males and females. One-way ANOVA was used to investigate the difference in vitamin D levels according to the seasons and age groups. Differences between each season and age group were compared with Tukey's honestly significant difference test. Nominal variables were compared using Pearson chi-square or Fisher's exact test. $P<0.05$ was considered statistically significant.

Results

The mean serum 25(OH)D level of 51,560 children was 22.86±16 (interquartile range: 15) ng/mL. Of the patients in this study, 28,309 (45%) were girls and 23,251 (55%) were boys. The mean serum 25(OH)D level was 25.1±16.6 ng/mL in boys, and 21.0±15.5 ng/mL in girls. Serum 25(OH)D levels were significantly higher in boys than in girls ($p<0.01$, Student's t-test). Of the patients, 20% (n=10,611) had vitamin D deficiency and 34% (n=17,385) had vitamin D insufficiency. It was determined that 61.4% (n=37,331) of girls and 45.6% (n=10,603) of boys suffered from vitamin D deficiency or

insufficiency. Vitamin D deficiency was 26.1% (n=7,424) in girls and 13.7% (n=3,187) in boys. Vitamin D insufficiency was 35.2% (n=9,969) in girls and 31.9% (n=7,416) in boys (p<0.01). There was a significant difference between serum 25(OH)D levels in terms of the age groups (p<0.01, ANOVA). The highest mean 25(OH)D levels were detected in infants (33.95 ng/mL) and the lowest in adolescents (18.3 ng/mL) compared with preschool and school-age groups. The mean serum 25(OH)D levels according to gender and age groups are shown in Table I.

Significant seasonal variability of 25(OH)D levels was detected (p<0.01, ANOVA). Summer and autumn had higher mean levels of 25(OH)D than winter and spring. Vitamin D deficiency was determined most frequently in winter with 30.7% followed by 28.4% in spring, 12.7% in summer, and 12.2% in autumn. In autumn, the prevalence of vitamin D deficiency (12.2%) or insufficiency (32.6%) was 44.8% in total giving the lowest seasonal percentage. In winter, 64.8% of children had vitamin D deficiency or insufficiency, and this was the highest percentage among the four seasons. The seasonal variation of 25(OH)D levels is shown in Table II. The frequency of vitamin D testing was observed to increase gradually. Vitamin D levels were examined in 8,834 children in 2015 and 27,282 in 2017 (Figure 1). A three-fold increase in 25(OH)D testing was determined over a 3-year period.

Multivariate regression analysis showed that being of adolescent age [odds ratio (OR): 6.98], being in the spring season (OR: 2.64) and being a girl (OR: 1.78) were significantly associated with vitamin D insufficiency (95% confidence interval) (Table III).

Discussion

Vitamin D deficiency is a serious public health problem worldwide. Vitamin D status has been intensively determined in different populations, including various ethnic and age groups in recent decades (12). In our study, vitamin D deficiency was determined at a frequency of 20% in our full study population. 26.3% of girls and 13.8% of boys had vitamin D deficiency consistent with the literature which reports higher vitamin D deficiency in the female gender (7). In this study, there was a gradual decrease in vitamin D levels with age after infancy. We found vitamin D deficiency at frequencies of 7.9%, 12.1%, 14.6%, and 29.8%, respectively in infancy, preschool, school, and adolescent age groups. In our study, the mean levels of 25(OH)D

Table I. Vitamin D level classification in children

Characteristics of children	Sufficiency >20 ng/mL		Insufficiency 12-20 ng/mL		Deficiency <12 ng/mL		p-value
	n	%	n	%	n	%	
Age groups							
Infant (0-2 years)	7,828	75.1	1,770	17.0	824	7.9	
Preschool (3-5 years)	3,478	53.4	2,235	34.4	789	12.1	<0.01
School (6-9 years)	4,185	47.5	3,331	37.8	1,290	14.6	
Adolescent (10-18 years)	8,073	31.3	10,049	38.9	7,708	29.8	
Gender							
Boy (n=23,251)	12,473	54.1	7,416	31.9	3,187	13.7	<0.01
Girl (n=28,309)	10,754	38.2	9,969	35.2	7,424	26.2	

Table II. Seasonal variation of serum 25(OH)D levels

25(OH)D levels	Sufficiency >20 ng/mL		Insufficiency 12-20 ng/mL		Deficiency <12 ng/mL		p-value
	n	%	n	%	n	%	
Spring (n=12,476)	4,555	36.5	4,378	35.1	3,543	28.4	
Summer (n=13,001)	6,998	53.8	4,355	33.5	1,648	12.7	
Autumn (n=13,969)	7,715	55.2	4,554	32.6	1,700	12.2	<0.01
Winter (n=12,114)	4,296	35.5	4,098	33.8	3,720	30.7	
Total (n=51,560)	23,598	45.7	17,385	33.7	10,611	20.6	

25(OH)D: 25-hydroxyvitamin D

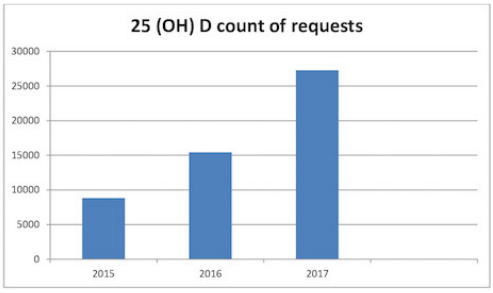

Figure 1. 25(OH)D count of requests according to years
25(OH)D: 25-hydroxyvitamin D

Table III: The effect of gender, age, and season in determining vitamin D insufficiency

	Adjusted OR (95% CI)	p-value
Gender		
Male (reference)		<0.01
Female	1.78 (1.72-1.85)	
Age group (years)		
0-2 (reference)		
3-5	2.82 (2.63-3.02)	<0.01
6-9	3.55 (3.33-3.78)	
10-18	6.98 (6.61-7.36)	
Seasons		
Autumn (reference)		
Winter	2.51 (2.38-2.64)	<0.01
Spring	2.64 (2.50-2.78)	
Summer	1.11 (1.05-1.16)	

OR: Odds ratio, CI: Confidence interval

were the highest in infants and the lowest in adolescents. Nearly 70% of adolescents and 25% of infants were found to have vitamin D deficiency or insufficiency. A daily 400 IU vitamin D supplement is provided to all infants during their first year in Turkey. This supplement may explain why we determined the lowest frequency in the infant group. As age increases, exposure to sunshine decreases due to spending more time indoors in front of a TV or computer. Insufficient playgrounds, the use of sunscreens with high sun protection factors, and covered clothing in adolescent girls have an influence on vitamin D levels (8,13). Vitamin D levels in adolescents may also have been found to be lowest for these reasons in our study. Preschool and school-age children have more chance to spend time outdoors than adolescents in our country because adolescents have to spend more time indoors preparing for exams in order to enter the college or university of their choice among the 2 million individuals they have to compete with.

In the HELENA study, vitamin D levels were determined to be below 30 ng/mL in approximately 80% of European adolescents and sufficient 25(OH)D levels were slightly higher in girls than in boys (22% versus 15%) (14). Bener et al. (15) reported vitamin D levels below 20 ng/mL in 61.6% of adolescents aged 11-16 years, 28.9% of schoolchildren aged 5-10 years, and 9.5% of preschool children under the age of 5 years in Qatar, which has ample sunshine. In a study from Afghanistan, vitamin D levels were reported to be <20 ng/mL in 61% of adolescents of whom 65% were girls. This result was speculated to be related to less sunlight exposure because of the wearing of traditional clothes and inadequate intake of vitamin D rich foods and supplements (13). The prevalence of 25(OH)D insufficiency among preschool children in Canada was found to be 51.7% in summer and 72.8% in winter (6). In another study from Canada, 14% of children aged 6-11 years had a plasma 25(OH)D concentration of <20 ng/mL (16). Pekkinen et al. (17) determined that 71% of Finnish children aged 7-11 years had vitamin D levels <20 ng/mL, despite having met or exceeded the recommended daily intake of vitamin D. Akman et al. (18) reported that vitamin D levels were below 20 ng/mL in 14.5% of children aged 1-7 years.

Vitamin D deficiency has been attracting more attention due to an increase scientific studies and frequent mentions in the media (19). The frequency of testing for vitamin D increased dramatically over an 11-year period in Australia (20). A six-fold increase in 25(OH)D testing was reported between 2007 and 2010 in the UK (8). We determined that there was increased vitamin D testing in Turkey during our study years. This may be because of increased awareness of vitamin D deficiency and its related diseases in recent years. Further evidence is needed to clarify whom to test in order to avoid over-testing and overdiagnosis.

In the literature, vitamin D deficiency has generally been found to be highest in winter or spring (5,21-23). The main factors suggested to be responsible for the seasonal variations of vitamin D are latitude and inadequate sunlight exposure during winter. Between November and February, above a latitude of 37°, there are evident decreases in the number of UVB photons reaching the earth. Furthermore, below a latitude of 37° and closer to the equator, more vitamin D3 synthesizes in the skin throughout the year (24).

Corrêa et al. (25) reported that vitamin D synthesis may reduce by 39% in high latitudes in their study regarding effective UV doses for vitamin D synthesis in

low (10.5°N-16.5°S), mid (23.6°S-34.6°S) and high latitudes (54.8°S-62.1°S). In Poland, at 50.3°N-53.4°N latitudes at the end of March, a serum concentration of 25(OH)D below 20 ng/mL was determined in 84.2% of children aged between 9 and 13 years (22). Vitamin D deficiency or insufficiency was reported to be 60.2% in one study involving Norwegian adolescents (Latitude 69°N) (26). In our study, Vitamin D deficiency (30.7%) or insufficiency (33.8%) were determined in 64.5% of the study group in winter in Ankara, which is the capital city of Turkey, at 39°N latitude.

Study Limitations

Our study has some limitations. The data was obtained from both healthy and sick children together and it was gathered retrospectively. Some patients may have diseases which affect vitamin D absorption and metabolism. Moreover, we do not know how much exposure to sunlight children got on a daily basis, their eating habits, their body mass index, or whether or not they took vitamin D supplements. Nevertheless, our study is valuable in being the largest epidemiological study to evaluate vitamin D status in children in Turkey.

Conclusion

Vitamin D deficiency or insufficiency was determined in more than half of all children in our study. Female gender, adolescence, and also the winter and spring seasons were found to be important risk factors for vitamin D deficiency or insufficiency. The frequency of vitamin D testing has increased dramatically over the years. Further evidence is needed to clarify whom to test. We propose that the Health Ministry pay attention to our study in order to develop a strategy or plan for vitamin D supplementation in adolescents, especially during the winter months.

Ethics

Ethics Committee Approval: The present study was approved by the Ethics Committee of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (15.05.2019/297).

Informed Consent: Informed consent was not obtained because this was a retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.S., Data Collection or Processing: G.Ç., Analysis or Interpretation: F.Z.Ö.Ç., Literature Search: E.A.A., Writing: E.S., E.A.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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J Pediatr Res 2021;8(4):444-50
DOI: 10.4274/jpr.galenos.2021.83604

Original Article

Pediatric Urethral Strictures and Management Strategies; An Evolving and Learning Experience

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ABSTRACT

Aim: Most of the surgical strategies for pediatric urethral strictures (PUS) are derived from adult experiences. Owing to this, we carried out this study to assess the management strategies for PUS in our institute.

Materials and Methods: This prospective study included 28 patients with PUS. Preoperatively, patients were assessed clinically and were subjected to voiding cystourethrography (VCUG) and pre-procedure cystoscopy. Intraoperatively, urethroscopy, VCUG and retrograde urethrography were used to evaluate the length of the stricture. Urethral dilatation (UD), direct visualization and internal urethrotomy (DVIU), excision and primary anastomosis (EPA) with or without pubectomy and dorsal onlay urethroplasty (DOU) were the procedures instituted to treat the strictures. After the procedure, a silicone catheter was left *in situ* for 1-2 weeks in cases of DU or DVIU and 4-6 weeks in cases of EPA or DOU. Postoperatively, patients were assessed in terms of their symptoms and for VCUG/cystoscopic evidence of reestablishment of urethral continuity. There was an average follow-up period of 1.9 years.

Results: Three patients were successfully treated with single session UD and another three with multiple sessions. Two UD patients required EPA. DVIU was performed in four patients. This procedure failed in one and so required EPA. EPA was carried out in fourteen patients with two requiring redo-EPA. Graft onlay urethroplasty was performed in five patients with satisfactory results.

Conclusion: The procedure to address a stricture should be tailored to the individual urethral anatomy, stricture length and the surgeons' experience. For smaller and partially obstructing strictures, DVIU and DU can be tried but these procedures seem to be less effective than EPA, with high rates of secondary procedures. However, if not accompanied by complete excision of fibrosed spongiosum, EPA may have to be repeated. For longer bulbar strictures, substitution urethroplasties are viable alternatives.

Keywords: Pediatric urethral strictures, urethral dilatation, direct visualisation and internal urethrotomy, excision and primary anastomosis

Introduction

Pediatric urethral injuries differ remarkably from adult urethral injuries. The pediatric urethra is short, immobile and inadequately protected by an immature pelvis thus making it susceptible to injuries (1). Posterior urethral injuries are more frequent than the anterior urethral injuries owing to the intraabdominal location of the bladder and the cranial placement of the prepubescent prostate (2). It has been observed that in pediatric pelvic fractures, 69% suffer prostatic urethral displacement compared to 42% in adults (3). Anterior urethra is less commonly involved with the bulbar urethra representing the most common area of anterior urethral injury in boys (1). Apart from this, there are instances of congenital urethral strictures which, though rare, are thought to be more frequent than suggested by

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Received: *03.11.2020* **Accepted:** *28.03.2021*

the literature (4). The consequences of pediatric urethral strictures (PUS) may be devastating and appropriate intervention is necessary for a successful outcome. Being rare, consensus over the best surgical approach for repair is lacking (5). In addition, most of the experience with these surgical approaches is derived from adult series. Owing to this, we conducted this study to assess the management strategies for PUS in our pediatric surgical unit.

Materials and Methods

This prospective study extended from November 2012 to November 2020 and was carried out with ethical clearance by the Institutional Ethical Committee and the receipt of informed consent from the legal guardians of the patients. Those patients in the pediatric age group operated on for urethral strictures were included in this study but those who did not complete a follow-up were excluded. The study period was 8 years. Preoperatively, all the patients were assessed clinically for symptoms such as dribbling, straining at voiding, retention of urine, dysuria and urinary tract infections. All the patients were subjected to voiding cystourethrography (VCUG) and pre-procedure cystoscopy. Intraoperatively, cysto-urethroscopy, VCUG and retrograde urethrography were carried out to evaluate the length of the stricture.

Urethral dilatation (UD), direct visualization and internal urethrotomy (DVIU), excision and primary anastomosis (EPA) and dorsal onlay urethroplasty (DOU, Barbagli technique) were the procedures performed to treat the strictures.

UD was done by metallic dilators and DVIU was performed by cold knife. EPA was performed via perineal midline incision followed by circumferential mobilization and the excision of fibrosed and scarred tissue. Tension free, epithelium to epithelium anastomosis was carried out after proper spatulation. Inferior pubectomy (pubic bone carving) was performed in patients when there was difficulty in approximating the urethral ends. DOU was also performed via midline perineal incision. After mobilization, the urethra was rotated 180 degrees, a longitudinal urethrotomy was carried out and buccal graft sutured in place.

An appropriate size silicone catheter was left *in situ* for 1-2 weeks in cases of DU or DVIU and 4-6 weeks in cases of EPA or DOU.

Postoperatively, patients were assessed at regular intervals for symptoms and their radiological investigations were recorded. Success was defined as the resolution of symptoms, successful initiation and completion of voiding with VCUG/cystoscopic evidence of the reestablishment of urethral continuity. The minimum follow-up was for six months and maximum for six years (mean follow-up: 1.9 years). Long term results with regards to erectile dysfunction are not yet known.

Results

Over a period of eight years, 28 patients were managed for urethral strictures. The median age of the patients was 6.5 years at the time of repair (range 3 months to 16 years). The most common etiology was trauma (Table I). Posterior urethra was involved more frequently (n=19, 67.8%) than the anterior urethra (n=9, 32.2%). Symptoms

Table I. Patient characteristics

Etiology	**Number of patients**	**%**
Traumatic	16	57.1
Motor vehicle accidents	13	46.4
Straddle injuries	3	10.7
Iatrogenic	7	25
Post PUV fulgration	5	17.8
Post-catherisation	1	3.6
Operated anorectal malformation	1	3.6
Idiopathic	2	7.1
Congenital	3	10.7
Location		
Posterior	19	67.8
Anterior	9	32.2
Symptomatology		
Diversion	15	53.5
Poor stream	10	35.7
Straining	9	32.1
Incomplete emptying	5	17.8
Dysuria	5	17.8
Urinary tract infection	4	14.9
Associations		
VUR	6	21.4
ARM	1	3.6
Seminal vesicle cyst	1	3.6
Solitary kidney	1	3.6
Pouch colon	1	3.6
Urethral diverticulum	1	3.6
VUJO	1	3.6

PUV: Posterior urethral valves, VUR: Vesicoureteral reflux, ARM: Anorectal malformation, VUJO: Vesicoureteric junction obstruction

and signs at the time of presentation are provided in Table I. Fifteen patients (53.5%) were on diversion in the form of suprapubic catheter or temporary vesicostomy when they were admitted to the unit. The associated comorbidities were vesicoureteral reflux, anorectal malformation, seminal vesical cyst, solitary kidney, pouch colon and urethral diverticulum. One patient with urethral diverticulum had a diverticulum in the anterior urethra, stricture in the posterior urethra and pouch colon.

The procedures undertaken were UD (n=8), DVIU (n=4), excision of the stricture with primary anastomosis (n=11) and DOU (n=5) (Table II). Single session UD was successful in 3 patients while the other five needed multiple sessions. Two of these patients eventually required EPA (Figure 1). DVIU was performed in four patients and it was unsuccessful in one who then required EPA. EPA were carried out in 14 patients including patients who underwent unsuccessful UD and DVIU. All the patients in the EPA group had posterior urethral strictures. Nine of the EPA-group patients had pelvic distraction injuries with complete disruption of the urethral lumen by a fibrotic tissue (Figure 2). These strictures were not negotiable by Terumo guidewire on urethra-cystoscopy. The initial two EPA patients developed recurrence requiring redo-EPA. These two patients had stricture lengths of 3.5 cm and 4.0 cm respectively. Graft onlay (DOU) procedures were done by Barbagli technique (Figure 3). Barbagli technique was performed in bulbar urethral strictures with compromised luminal patency. All of these patients are currently symptom free. Patients were followed up for at least 6 months and up to six years with a mean follow-up period of 1.9 years. The long-term results with regards to erectile dysfunction are not available to date.

Discussion

Urethral strictures in pediatric patients, though uncommon, can be very distressing for the patients and their care-givers (5). Urethral trauma leading to strictures is usually sustained by pelvic fractures due to motor vehicle accidents (6,7). The reported incidence of urethral injury in pelvic traumas for boys ranges from 7.4% to 13.5%

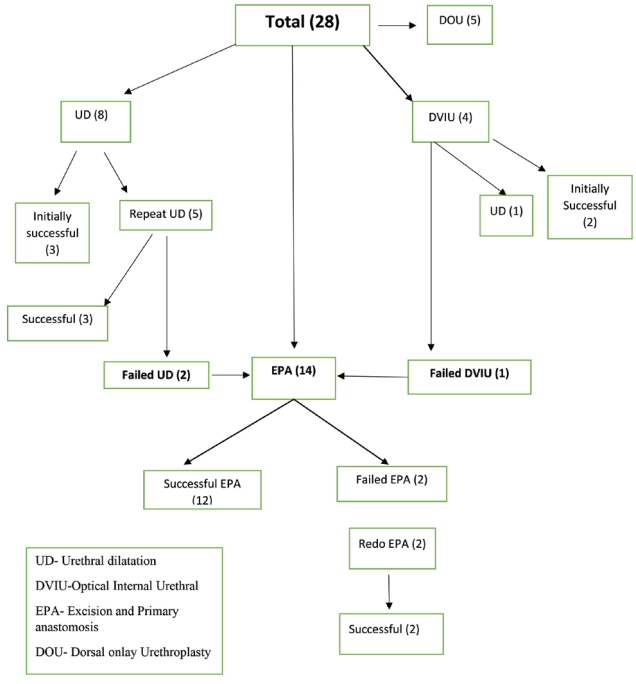

Figure 1. Schematic representation of the current study

Table II. Stricture characteristics and procedures adopted

Procedure	Number of patients	Region of urethra involved (n)	Etiology (n)	Mean stricture length (n)	Secondary procedures
UD	8 (28.6%)	Ant. (2), Post. (6)	Congenital (1) Traumatic (4) Iatrogenic (3)	Not mentioned (4) Point stricture (4)	EPA in 2 patients
DVIU	4 (14.3%)	Ant. (2), Post. (2)	Congenital (1) Idiopathic (1) Iatrogenic (2)	0.4 cm	EPA in 1 patient
EPA	11 (39.3%)	Post. (11)	Traumatic (10) Iatrogenic (1)	2.2 cms	Redo EPA in 2 patients
Dorsal onlay urethroplasty	5 (14.3%)	Ant. (Bulbous) (5)	Idiopathic (1) Congenital (1) Iatrogenic (1) Traumatic (2)	3.8 cm	None

UD: Urethral dilatation, DVIU: Direct visualization and internal urethrostomy, EPA: Excision and primary anastomosis, Ant: Anterior, Post: Posterior

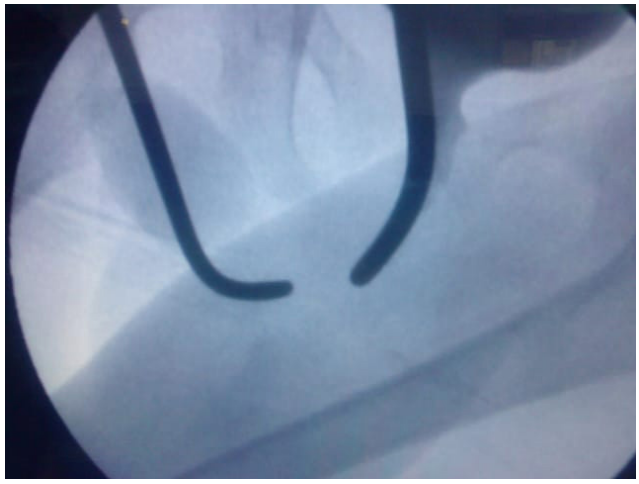

Figure 2. Pelvic distraction injury with complete disruption of urethral lumen

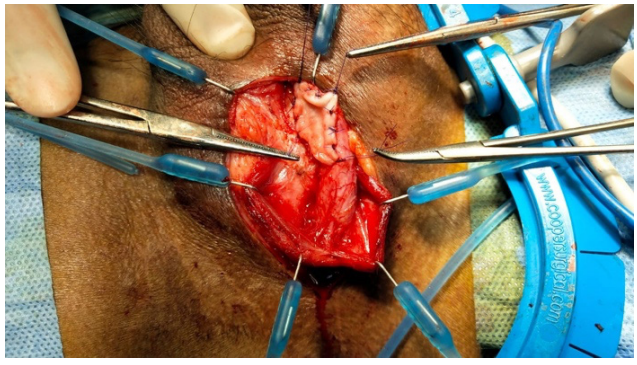

Figure 3. Dorsal onlay urethroplasty

(8). In our study, the most common mode of urethral injuries and subsequent strictures was also due to pelvic trauma acquired by motor vehicle accidents or straddle injuries (Table I). Iatrogenic trauma was a cause in 7 (25%) patients with more than half of them (n=5) reporting after posterior urethral valve fulguration. Posterior urethral valve fulguration can lead to stricture formation in 0-25% of patients (9). This situation is largely preventable if the necessary technical precautions are taken during the procedure. Post-fulguration strictures have usually been reported after the excessive use of diathermy, dry fulgurations in vesicostomies or disproportionate instrumentation in neonates (10). As in our study, the other iatrogenic mechanisms for urethral strictures are urethral catheterization and surgery for anorectal malformation (5,7). Congenital and idiopathic strictures were seen in 3 and 2 patients respectively. Congenital urethral strictures are rare, although the exact prevalence still remains unclear (4). CUS are seen in infancy and early childhood in association with other structural anomalies (11). In a significant number of older patients, there is no obvious cause and such cases are labeled as idiopathic strictures (12). The possible cause of idiopathic strictures is thought to be unrecognized trauma (13).

As in our study, posterior urethra is more frequently involved than anterior urethra. The peculiar anatomy of pediatric urethra makes it more susceptible to trauma and stricture development. In the anterior region, bulbar urethra is the most vulnerable to trauma and subsequent stricture formation due to straddle injury. Due to straddle injury, the bulbar urethra can be compressed against the inferior aspect of the symphysis pubis resulting in trauma and stricture formation (1).

Most posterior urethral strictures are managed by suprapubic cystostomy and delayed repair, though some would favor early primary repair (14). However, an increased incidence of impotence and incontinence has been cited to preclude early primary repair (1,15) and in light of this, our unit follows a protocol of delayed repair. Fifteen (53%) patients of our PUS were on suprapubic diversion and the rest presented with lower urinary tract symptoms, predominantly with poor stream (n=10, 35.7%) and straining (n=9, 32.1%). It is also worth mentioning two patients who had unusual anomalies. One of them had a congenital urethral stricture with a seminal vesical cyst, and the other one had congenital posterior urethral stricture combined with anterior urethral diverticulum, pouch colon and vesicoureteral reflux. Congenital urethral strictures are known to be associated with other anomalies but associations like pouch colon and seminal vesical cyst are hitherto unknown though hypospadias and prostatic anomalies are very well reported in the literature (16).

Quite a few procedures were applied in the management of patients with urethral strictures. UD was successful in 3 (37.5%) patients with one session. Five (62.5%) patients received multiple sessions of UD. Of these patients, two patients did not achieve the desired outcomes and so they underwent EPA. UD is the initial management tool for urethral strictures (17). Its success rates are reported to be variable with a stricture recurrence rate of 67-78% over a 6-year period (18). Nonetheless, combined with DVIU, it definitely has a role to play in the treatment of short strictures especially in congenital and idiopathic strictures in infants (12). DVIU is reported to have similar success rates (50-60%) as DU (18). In our experience, DVIU was successful in two of the four patients (50%) after the initial procedure. One patient was symptom free only after a secondary UD. Early recurrence was observed in another patient who underwent EPA later on. DVIU is a quick and

easy procedure and is primarily useful in short segment (<2 cm) strictures (6,18). The utility of this technique in the management of recurrent strictures has been questioned but still UD and DVIU, being technically easy and quick, remain the two most frequently performed procedures for smaller urethral strictures (19) despite the better reported results of EPA. EPA involves excision of a urethral stricture along with fibrotic spongiosum (Figure 4 and 5) through a perineal midline or inverted Y-shaped incision. The reported success rates with this technique approach 86% and thus it may be considered as the optimal treatment of short segment (2-3 cm) stricture (20). In our study, 14 patients (mean stricture length of 2.2 cm) underwent EPA including three patients who had had unsuccessful UD and DVIU. Twelve patients (85.8%) became symptom-free after the procedure while two patients continued to have obstructive symptoms with persistently raised post-void residual on ultrasonography. On further evaluation and repeat VCUG, both of these patients were shown to have recurrent strictures and were hence re-operated. Both required redo-EPA with inferior pubectomy for re-coursing the urethra without causing penile chordee. Following the redo-EPA procedure, both patients had satisfactory results although one had intermittent bouts of stress incontinence. It is worth mentioning here that both of these patients had primary repair done during our early experience working with these procedures. Subsequently, with greater experience and from the critical feedback of stalwarts in the field, we realized that partial and incomplete excision of fibrosed spongiosum was responsible for the recurrences, and this was rectified in subsequent procedures. EPA is a technically demanding procedure especially in the pediatric pelvic configuration and it has a steep learning curve (21,22). Yet after the initial two failures, all twelve EPA patients had satisfactory results in terms of symptom improvement and micturition stream on VCUG. Cystoscopy at 6 weeks revealed a patent urethra in all of them (Figure 6). As none of the procedures is an ideal solution for PUS, EPA also comes with its own set of issues. We encountered stress incontinence in two patients and increased frequency in two patients, which were subtle and non-worrying for the patients and thought to be due to some amount of sphincter damage in high posterior urethral strictures.

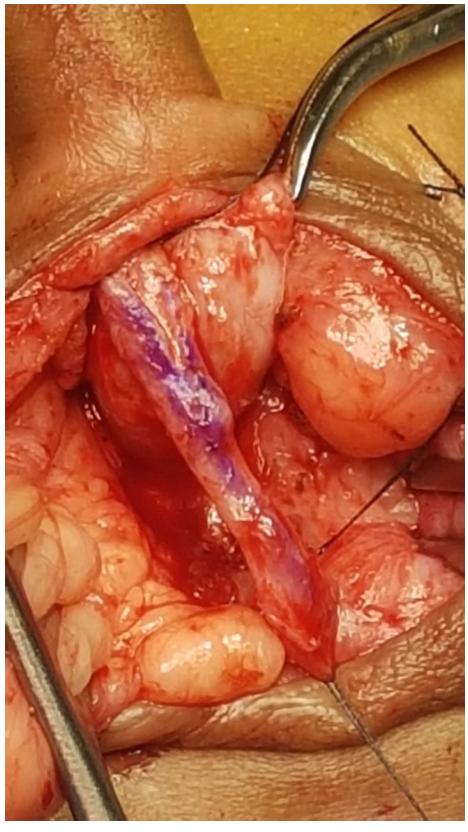

Figure 4. Mobilization of urethra for excision and anastomosis

However, ejaculatory dysfunction, decreased glans sensation, chordee and erectile dysfunction have been reported in the literature as some of the main complications of EPA (20). Sexual complications after EPA are reportedly higher than for buccal urethroplasty patients, although the buccal group usually have much longer strictures (23). Buccal mucosa may be used as ventral or dorsal onlay graft. We performed dorsal onlay procedure in five patients. Three patients received buccal mucosal grafts and one received anterior urethral strip as a dorsal onlay graft. This last patient was also the patient with anterior urethral diverticulum and posterior urethral stricture. Urethral strip from the diverticulum was used as an onlay graft for the

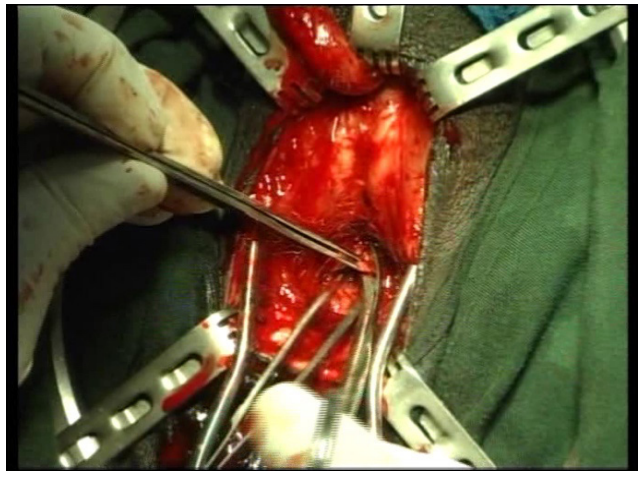

Figure 5. Excision of fibrosed spongiosum being carried out. Complete excision of fibrosed spongiosum is key to success in EPA
EPA: Excision and primary anastomosis

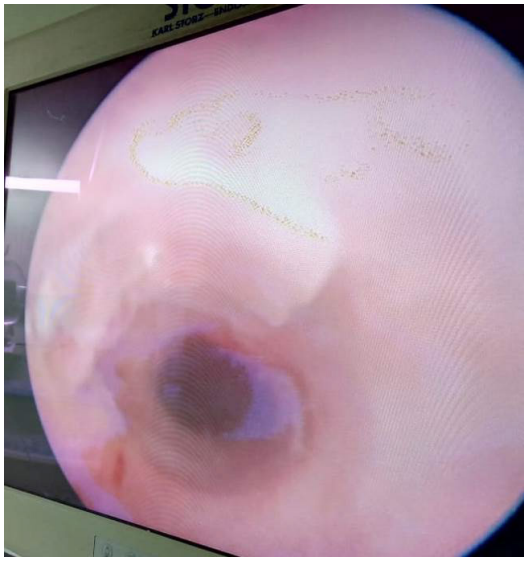

Figure 6. Check cystoscopy in a patient of EPA showing patent urethra
EPA: Excision and primary anastomosis

posterior urethral stricture. All these five patients had satisfactory results in the postoperative period. Since the early 1990s, buccal mucosal graft has been the most used graft material for substitution urethroplasty. The overall success rates of onlay graft urethroplasty are about 90% when used in the bulbar urethra (20).

Conclusion

Pediatric urethral strictures have a diverse etiology of which trauma is the most common. The procedure to address a stricture should be tailored to the individual urethral anatomy, stricture length and the surgeon's experience. For smaller and partially obstructing strictures, DVIU or DU can be tried but these seem to be less effective than EPA, with high rates of secondary procedures. However, if not accompanied by complete excision of the fibrosed spongiosum, EPA may have recurrences. For longer strictures, substitution and urethroplasties are viable alternatives.

Ethics

Ethics Committee Approval: This prospective study extended from November 2012 to November 2020 after ethical clearance by institutional ethical committee.

Informed Consent: Informed consent was obtained from the legal guardians of the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Design: M.S., Data Collection or Processing: M.F.H., Analysis or Interpretation: V.J., N.M., Writing: M.F.H.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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J Pediatr Res 2021;8(4):451-5
DOI: 10.4274/jpr.galenos.2021.21447

Original Article

Awareness of FMF among Caregivers

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ABSTRACT

Aim: Familial Mediterranean Fever (FMF) is one of the most frequent genetic diseases with a frequency of 1/1,000 in our country. We aimed to assess awareness of FMF among caregivers of patients with and without FMF.

Materials and Methods: Caregivers of FMF patients (group 1) and other caregivers who were in hospital for other reasons (group 2) were given a questionnaire regarding FMF and the results were compared between the 2 groups.

Results: The mean ages were similar between group 1 (n=142) and group 2 (n=207). Female gender and lower educational status were more frequent in group 1. Group 1 was more aware that recurrent fever, joint pain, abdominal pain, and its occurrence in attacks are seen in FMF; and also that the disease is inherited rather than contagious; that a specific treatment exists; that the risk of kidney and heart failure increases when not treated; that attacks are triggered by sleeplessness, tiredness or emotional stress; that colchicine does not provide complete recovery; and that diarrhea is the most common side effect of colchicine ($p<0.05$). However, awareness about chest pain as a feature, infertility as a complication, non-adherence as a trigger for the disease and the statement that "patients feel healthy between attacks" were similar ($p>0.05$). Interestingly, group 2 was more aware that different treatment options exist ($p=0.04$). The total score was higher in group 1 and in participants who only graduated from secondary school or less ($p<0.01$).

Conclusion: Being a caregiver of a patient was associated with a higher level of awareness of FMF regardless of education level, however, they still need to be informed about current developments.

Keywords: Familial Mediterranean Fever, awareness, caregivers

Introduction

Familial Mediterranean Fever (FMF) is an autosomal recessive disease characterized by recurrent episodes of fever, peritonitis, pleuritis, arthritis and erysipelas-like skin lesions. It is the most common form of hereditary autoinflammatory disorders (1,2). The estimated prevalence of FMF is 1/1,000 and the carrier rate is 1:5 in our country, Turkey (1,3).

The most common complication of FMF is secondary amyloidosis. To avoid complications, both clinicians and the general population should be well-informed. With the increased awareness of physicians, the diagnosis of the disease and the prescription of colchicine, which has been reported as the standard of care for prevention of attacks and secondary amyloidosis, has increased. As a result, the rates of patients with amyloidosis have decreased over time (4). In a previous study, it was indicated that only 18% of the population in the third largest city of our country where this study was conducted were aware of this disease (5).

In this study, we aimed to evaluate and compare the awareness levels of the caregivers of those patients diagnosed

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Received: *07.03.2021* **Accepted:** *29.03.2021*

with FMF and the caregivers of other children admitted to outpatient clinics. This study was carried out via a face-to-face questionnaire conducted by volunteer medical school students. In this way, it was planned to also raise awareness and more thoroughly inform caregivers about FMF by giving the correct answers to the questionnaire questions at the end of the interview to all study participants.

Materials and Methods

This study was approved by the İzmir Katip Çelebi University, Non-Invasive Clinical Research Ethics Committee (17.01.2018/16). The caregivers of those patients who were being followed up in pediatric nephrology and pediatric rheumatology outpatient clinics with a diagnosis of FMF and the caregivers of other outpatients between April 2018 and October 2018 were enrolled in this study. All participants completed a questionnaire including personal information about age, gender, occupational and educational status and 17 additional questions about complaints regarding FMF disease, its way of transition, its treatment options and possible complications. At the end of the questionnaire, they all agreed to the statement that their data could be used in scientific studies and signed the form. Educational status was categorized as "graduated from elementary school", "graduated from secondary school", "graduated from high school", or "graduated from academy/university". While selecting participants other than the caregivers of FMF patients, we asked the question "Have you ever heard about FMF disease?" and continued with the questionnaire with those who answered the question positively. The questionnaire was conducted by volunteer medical school students via a face-to-face method. The students were informed about the answers of the questionnaire and they were asked to subsequently share the correct answers with the participants.

The first question was about any first-degree relatives of the participants diagnosed with FMF including their own selves. All except one of the following questions had the two options of "yes" or "no". The next five questions asked whether the patients had recurrent fever, abdominal pain, joint pain, chest pain or complaints that appear with attacks. The following two questions were about the transition of the disease. They asked whether FMF was a contagious disease or whether it was inherited and consanguinity played a role. The rest of the questions were about treatment options and complications. They asked whether there was a drug specifically used in FMF; whether FMF caused renal failure, cardiac failure or infertility; whether attacks were triggered by sleeplessness, tiredness, emotional stresses and/or by missing the treatment; whether patients felt healthy between the attacks; whether there was a complete cure with colchicine; and whether there was any other treatment option. The only question having two different options was the one which asked about the most common side-effect of colchicine being either vomiting or diarrhea. One point was given to each correct answer and a "total score" was calculated for each participant.

The caregivers of our patients with FMF constituted the study group (group 1) and the others formed the control group (group 2). However, among the control group, those individuals diagnosed with FMF themselves or those who had first-degree relatives diagnosed with FMF whom they take care of were transferred into the study group. While answering the questions, participants in group 1 were asked to evaluate the features of the disease in general rather than personally. The correct answers and total scores were compared between the groups.

Statistical Analysis

Statistical analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL). Descriptive statistics are shown in mean ± standard deviation and frequency format. Continuous variables between the groups were compared by Student's t-test, and categorical variables were compared with chi-square test. A "p" value of <0.05 was considered significant in all statistical evaluations.

Results

A total of 349 volunteers participated in this study. Of these, 114 were the caregivers of patients with FMF and 235 were the caregivers of other outpatients. Twenty-eight of the latter group (12%) had a relative with FMF whom the individual took care of or they had been diagnosed with FMF themselves. Thus, 28 individuals were transferred to group 1. Finally, group 1 consisted of 142 and group 2 consisted of 207 patients.

When the demographic findings were compared, the ages were similar between the groups. Female gender and an education level of only graduating from secondary school or less was more common in group 1 (Table I). When the rates of correct answers were compared between the groups, the

Table I. Comparison of the demographic findings between the groups

	Group 1 (n=142)	**Group 2 (n=207)**	**p-value**
Age (Year)	37.68±8.11	36.46±10.2	0.238
Gender (Female)	103 (73%)	123 (59%)	**0.04**
Education (Secondary education level or less)	107 (75%)	41 (20%)	**<0.01**

rate of awareness that recurrent fever, abdominal pain and joint pain are observed in FMF was higher in group 1, while expectancy for chest pain was similar between the groups. Participants in group 1 were more frequently aware that FMF occurs in attacks, is not a contagious disease being transmitted genetically, and that a specific drug exists for the treatment of FMF. In addition, group 1 was more frequently aware that FMF may cause renal and cardiac failure. However, the rate of awareness that FMF may cause infertility was similar between the groups. Group 1 was more likely to be aware that sleeplessness, tiredness and emotional stresses may trigger attacks. Participants in both groups were similarly aware in high rates that missing treatment may trigger attacks and that patients feel healthy between attacks. Group 1 was more aware that patients cannot be totally cured with colchicine and the most common side effect of colchicine is diarrhea, as expected. However, contrary to expectations, group 2 was more aware that there are different treatment options other than colchicine (Table II).

Group 1 had a significantly higher total score when compared with group 2. When educational status was analyzed, there were 148 patients who had only graduated from secondary school or less and there were 201 participants who had continued their education beyond secondary school. The "total score" was interestingly higher in those participants who had only graduated from secondary school or less (12.87±2.74 vs. 11.66±2.7; p<0.01). Explaining this situation, it was observed that those participants belonging to group 1 were more frequently from those who had only graduated from secondary school or less (72% vs. 17%, p<0.01).

Discussion

This study, based on a questionnaire carried out by volunteer caregivers determined that individuals who were

Table II. Comparison of the rate of correct answers to the questions between the groups

Questions	Group 1 (n=142) (n, %)	Group 2 (n=207) (n, %)	p-value	Previous study (n=524) (%)
Recurrent fever	135 (96)	161 (78)	**<0.01**	84
Abdominal pain	138 (97)	170 (82)	**<0.01**	47
Joint pain	137 (97)	141 (68)	**<0.01**	54
Chest pain	93 (66)	115 (56)	**0.067**	25
Appears with attacks	139 (98)	152 (74)	**<0.01**	
Contagious	135 (95)	160 (77)	**<0.01**	
Inherited and consanguinity play a role	121 (86)	141 (68)	**<0.01**	78
Causes renal failure	134 (94)	121 (58)	**<0.01**	78
Causes cardiac failure	86 (61)	103 (50)	**0.042**	26
Causes infertility	69 (51)	93 (46)	0.412	Male infertility: 28 Female infertility: 42
Specific medication exists for FMF	133 (99)	160 (77)	**<0.01**	72
Sleeplessness, tiredness and stress trigger attacks	127 (89)	160 (78)	**0.009**	Sleeplessness: 56 Tiredness: 61 Emotional stress: 69 Infections: 63
Non-adherence to treatment triggers attacks	129 (91)	182 (89)	0.522	81
Patients feel healthy between attacks	91 (64)	127 (62)	0.727	
Total cure with colchicine?	90 (64)	102 (50)	**0.012**	
Most common side effect? Vomiting? Diarrhea?	99 (74)	106 (53)	**<0.01**	
Is there any different treatment option other than colchicine?	66 (49)	133 (65)	**0.004**	
Total score	13.54±2.19	11.24±2.76	**<0.01**	

FMF: Familial Mediterranean Fever

diagnosed with FMF or those who were taking care of a patient diagnosed with FMF were more aware of the disease, as expected. However, we observed that these caregivers were not well-informed that patients may have chest pain during attacks, FMF may cause infertility or that patients feel healthy between attacks. In addition, it was demonstrated that regardless of their level of education, responsibility for the primary health care of a patient with FMF provided a higher level of knowledge about the disease.

In our study, the mean ages of the participants in both groups were similar. However, female gender was more frequent and lower educational status was more common in group 1. A previous study was conducted on volunteers visiting a mega shop in our city (excluding those diagnosed with FMF and those who were medical doctors). It can be considered that this sample group included participants from all socio-economic levels. In this sense, it can be thought that the population of that study and our participants in group 2 are comparable.

FMF is characterized by recurrent episodes of fever and sterile inflammation resulting in abdominal pain caused by peritonitis, chest pain caused by pleuritis, and joint pain caused by arthritis. In the largest cohort from our country, the frequency of features of FMF were described as follows: fever 92.5%, peritonitis 93.7%, pleuritis 31%, arthritis 47.4%, arthralgia 49.7%, erysipelas-like erythema 20.9%, myalgia 39.6%, protracted febrile myalgia 2.3%, and protracted arthritis 2.6% (1). The most widely used adult criteria to diagnose FMF is the Tel Hashomer criteria (6). However, since the specificity was as low as 54.6% in children, the Yalcinkaya et al. (7) criteria was proposed for children in 2009. This set of criteria (7) and the most recent classification criteria (8) for FMF includes fever, abdominal pain, chest pain, arthritis and family history of FMF. Since the most frequent complaints reported in the nationwide cohort and proposed in the criteria were fever, abdominal pain, chest pain and arthralgia, we preferred to ask about these complaints in the questionnaire. Although myalgia has become a more recognizable feature of FMF (9), we did not put it among the options. As expected, group 1 was more aware that those patients with FMF have recurrent fever, abdominal pain and joint pain during attacks. However, information about chest pain was not well-known in group 1 with a rate of only 66%, which was not different from the control group. This may be related to the fact that chest pain appears less frequently. In the previous study, although it is not possible to make a statistical analysis, the rate of awareness about the complaints of FMF were apparently lower, other than for recurrent fever, when compared to group 2 (Table II).

It is well-known that FMF is an autosomal recessive disease and consanguinity also plays an important role in its transition. In the largest nationwide survey from our country, the consanguinity rates ranged between 15% and 26% in different regions (1). Group 1 was more aware about the transmission of the disease than group 2, as well as the recent study participants.

Amyloidosis, which is the most undesirable complication of FMF, mainly affects the kidneys but it may also affect the heart (10). In addition, infertility is one of the most important long-term complications of FMF for both sexes. Infertility is more common in female patients, those with FMF disease onset <20 years, those with higher disease severity score, and colchicine non-response (11,12). The caregivers of our patients were aware about the complications of FMF including renal and cardiac failure. However, we noticed that infertility was not well-known among them as it also was not well-known in the control group or among the participants of the previous study.

The most frequent triggering factors for FMF were defined as tiredness, emotional stresses, cold exposure and menstruation in females (13,14). In addition, standing up for a long duration, long-duration travel or infection may precede attacks. Non-adherence to colchicine is another triggering factor for attacks (15). In our questionnaire, we asked whether sleeplessness, tiredness, emotional stresses and non-adherence to treatment may trigger the attacks. Group 1 was more aware of the triggering factors and all the participants were well-aware that non-adherence is another risk factor. This may be due in part to the way the question was asked. It is logical that non-adherence is an associated factor for risk.

In between episodes, affected individuals are usually symptom-free and feel healthy (16). However, only 64% of the caregivers of our patients think in the same way. Interestingly, the rest of them thought that their children feel weak and tired most of the time even in non-attack periods.

FMF requires regular medication. Colchicine is an ancient drug proven to be effective in the prevention of recurrent inflammatory episodes and the development of amyloidosis in FMF (17). However, it has a narrow therapeutic margin. Its dose-dependent side-effects on the gastrointestinal system (increased motility, diarrhea, abdominal pain and vomiting) limit its use at toxic doses (17). Its most common adverse effect is diarrhea (18). As expected, almost all the participants in group 1 were aware that a specific treatment exists for FMF, and the other groups were able to give the correct answer in closed ranges. Group 1 answered the

question correctly that colchicine cannot provide a complete cure and the most common side-effect is diarrhea.

In patients unresponsive to colchicine, interleukin-1 blockade provides an effective and safe way to suppress inflammation (17). It has become an increasingly popular treatment nowadays. Interestingly, not the primary caregivers of our patients with FMF, but the other participants were more frequently aware that there are other options apart from colchicine for FMF. We consider that we have not been able to inform the caregivers of our patients well enough. We had the opportunity to inform the caregivers and patients about the alternative options in colchicine resistant or intolerant cases.

Study Limitations

Our study has some limitations. The number and educational status of the patients in the groups were unequal. However, it was thought that our study can contribute to the literature, since the number of similar studies is limited. As a face-to-face method was used for the questionnaire, we had the opportunity to inform the families of the right answers at the end of the process. In addition, this study improved the ability of the students to design and perform a study and their own awareness about FMF. They also had the chance to observe the deficiencies of the primary caregivers in such a frequent disease.

Conclusion

Finally, we concluded that being close to a patient provides a higher level of awareness about FMF regardless of one's level of education. In addition, we noticed that even the primary caregivers can be unaware of well-known details and current developments. Thus, FMF caregivers and patients should be given accurate and up-to-date information whenever possible.

Ethics

Ethics Committee Approval: This study was approved by the İzmir Katip Çelebi University, Non-Invasive Clinical Research Ethics Committee (17.01.2018/16).

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Design: B.K.D., T.K., G.Y., E.S. Data Collection or Processing: T.K., G.Y., Analysis or Interpretation: B.K.D., E.S., Literature Search: B.K.D., Writing: B.K.D., T.K., G.Y., E.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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J Pediatr Res 2021;8(4):456-61
DOI: 10.4274/jpr.galenos.2021.97720

Original Article

The Effect of Noise Meters Giving Visual and Auditory Alarms Used on Reducing Noise in Neonatal Intensive Care Unit

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ABSTRACT

Aim: This study was conducted to determine the effect of the use of a noise meter emitting visual and auditory alarms on reducing noise.

Materials and Methods: The study was conducted in an experimental design in a hospital in a Neonatal Intensive Care Unit (NICU). In the study, a noise meter emitting visual and auditory alarms and a digital noise meter were placed in a room (group 1); whereas, in the other room, only a digital noise meter was placed (group 2). The noise meter emitting visual and auditory alarms was hung on the most visible wall in the room and thus visual and auditory alarms were provided to the staff members in the room. The digital noise meter was hidden behind a closet in the same area in both rooms. The noise levels of the rooms were measured via the digital noise meter in both rooms in a way that data would come in continuously for two weeks.

Results: It was found that the total mean noise level in group 1 was significantly lower than group 2 for the two weeks ($p<0.01$). It was determined that the noise levels on weekdays and at the weekend were significantly lower in group 1 than group 2 in week 1 ($p<0.01$); whereas, in week 2 there was no difference between the groups in terms of the noise levels on weekdays and at the weekend ($p>0.05$).

Conclusion: The use of a noise meter emitting visual and auditory alarms might be effective in reducing noise in NICUs.

Keywords: Neonatal intensive care, newborn, noise, nursing, sound

Introduction

Individualized developmental care is an approach aiming at reducing the stress of newborns staying in neonatal intensive care units (NICUs) and offering relevant nursing interventions (1). In addition, it defines the physical, psychological, and emotional weaknesses of infants and their families and aims to minimize short-term and long-term possible complications associated with hospital experiences (2). The founder of modern nursing, Florence Nightingale, formed the basis of developmental care with her words, "Nurses have responsibilities in creating and maintaining the environment which is a great help in the recovery process" (2). Physical, humanitarian, and system components forming the remedial environment are crucial to develop evidence-based applications for quality care (3,4).

NICU nurses should be able to protect high-risk newborns from the sensorial stimuli which create toxic stress within the physical environment (3-5). In order to protect high-

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Received: *08.12.2020* **Accepted:** *20.04.2021*

risk newborns from noise in the sensorial environment, the ambient noise level in a NICU is recommended to be below 45 decibels (dB) by the American Academy of Pediatrics (AAP) (6). However, in most studies, it was reported that the noise level was above 45 dB and often between 53-62 dB (7-10). In the study of Kol et al. (11), daytime noise levels were found to be higher in the NICU than at night.

Noise is a stressor for newborns. When a preterm newborn is exposed to noise in the NICU, it may give physiological and behavioural reactions depending on the increased stress. Studies report that preterm infants who are exposed to noise may develop problems such as a decrease in heart rate (12-14) and blood pressure in the cardiovascular system; a decrease in oxygen saturation (12,13) and respiratory rate (15) in the respiratory system; apnoea and a decrease in heart rate and brain perfusion depending on hypoxia (15,16); sleep disorders (13,17) and problems in long-term neurodevelopment; problems in language development (18) and hearing (19).

There are many ways to reduce noise. These methods include the use of sound-absorbing panels (20), ear plugs (18) and earmuffs (17), noise-reducing programs (7,8,21-23), restructuring the unit structure (24,25) and personnel behavioural change (8). In addition, it has been reported that the use of noise meters giving a visual alarm may also be effective in reducing noise (26-29). However, we did not find any study in the literature on noise meters emitting visual and auditory alarms. All of these above mentioned methods serve to reduce noise in a NICU. Since noise has many negative effects on the newborn, it is very important to protect them in the NICU from the noise of the environment. The purpose of this study was to determine the effect of the use of noise meters which emit visual and auditory alarms on noise reduction in a NICU.

Materials and Methods

Design and Setting

This study was conducted with an experimental design in a hospital in the NICU between December 2017 and January 2018. There were totally five rooms in the unit. The first and second rooms both had nine incubators and other devices such as ventilators, monitors and pumps and a sensor-fitted door according to the patient's condition. These two rooms were both 56 m^2. The third room was a sepsis room with a total of eight sections and eight incubators. The fourth room was 66 m^2 and had twelve incubators. The fifth room was a mother-infant adaptation room with four sections and eight incubators. The study was conducted in the first and second rooms of the unit as they had the same square meter.

Hypothesis: The noise meter emitting visual and auditory alarms used in NICU;

H_0: does not affect noise level.

H_1: reduces ambient noise level.

Sample

The population of this study consisted of all the staff members in the unit (doctors, nurses, secretaries, personnel and visitors). A total of 72 individuals (five doctors, 53 nurses, four secretaries, and 10 personnel) were working in the unit. They worked in shifts in the two rooms where the study was conducted.

Measurements

Noise Meter Emitting a Visual and Auditory Alarm

The device had an alarm system with three colours (red, yellow, and green) indicating the noise level. It could be regulated with a control button at 50 dB and 110 dB levels and at ten-decibel intervals. The device gave a green visual alarm between 50-60 dB and a yellow visual alarm between 60-70 dB. It gave a red visual and auditory alarm above 70 dB (Figure 1). The device emitted visual and auditory alarms and it was expected that the unit staff would change their behaviour in terms of reducing the noise due to these warnings.

Figure 1. Noise meter which emits a visual and auditory alarm and a digital noise meter

Digital Noise Meter

This device was set between 30-130 dB. The noise level was measured via the device in a way that data would be recorded every two seconds. The data in the device memory was transferred to a computer via a USB cable (Figure 1).

Procedure

In the study, a noise meter emitting visual and auditory alarms and a digital noise meter were placed in one room (group 1), whereas, in another room, only a digital noise meter was placed (group 2). At the beginning of this study, the staff members in the unit were informed about the study. The noise meter emitting visual and auditory alarms was hung on the most visible wall in the room and thus visual and auditory alarms were provided to the staff members in the room for two weeks. The digital noise meter was hidden behind a closet in the same area in both rooms. The noise levels of the rooms were measured via the digital noise meter in both rooms in a way that the data would be recorded continuously every two seconds for two weeks.

Ethics committee approval (date: 11/29/2017; No: 488) from İstanbul Medipol University Ethics Committee as well as institutional permission was obtained for this study.

Data Analysis

The results obtained in the study were assessed using the IBM SPSS Statistics 22 and R-3.5.2 program (30) for statistical analyses. Whether or not the variables were normally distributed was assessed via the Kolmogorov-Smirnov test. The paired sample t-test was used in assessing the data on weekdays and at the weekend and in the daytime and night. The student t-test was used in assessing the measurements in group 1 and group 2. Significance was assessed at a level of $p<0.05$.

Results

When examining the total noise level for two weeks, it was found that the mean noise level was significantly lower in group 1 than group 2 ($p<0.01$) (Table I).

Table I. Evaluation of total noise measurements with noise meters giving visual and auditory alarms and digital noise meter

Rooms	**M ± SD**
Group 1	69.92±1.41
Group 2	70.38±1.43
t	**-3,144**
p	**0.002****

t: Student-t test, **p<0.01
SD: Standard deviation

When assessing the weekly noise for two weeks, it was determined that the noise levels on weekdays and at the weekend were significantly lower in group 1 than group 2 in week 1 ($p<0.01$); whereas, in week 2 there was no difference between the groups in terms of the noise levels on weekdays and at the weekend ($p>0.05$) (Table II).

When comparing group 1 and group 2 within themselves; it was observed that in group 1 the noise level was significantly lower on weekdays and remained the same at the weekend in week 1, whereas in group 2 the noise level was significantly lower at the weekend and remained the same on weekdays in week 2 (Table II).

Discussion

Newborns are exposed to intense noise throughout their stay in NICUs. The major source of noise is reported to be human-made sounds (31,32). Newborns in NICUs get consistently exposed to sounds at a higher frequency than they would ever encounter in intrauterine life, which affects the nervous system development of preterm infants negatively (33). Studies report that noise may cause hearing impairment, sleep disorder, irritability (34), physiological imbalances in heart rate (12-14), respiratory rate (15), blood pressure (14) and oxygen saturation (12,13), as well as irritation, agitation, crying, hypoxia and even minimal intracranial haemorrhage in newborns (35).

AAP has reported that noise levels in NICUs should be below 45 dBA in the daytime and below 35 dBA at night to provide a deep sleep, to assist the awake-asleep cycle and to protect newborns physiological stability (6,36). However, in numerous studies, this limit was seen to be exceeded (7-10,37). In the measurements conducted in the present study, it was found that while the lowest noise level was 68.01±2.15 dBA, the highest noise level was 71.67±1.19 dBA (Table I, II). According to this result, the noise levels determined in the NICU were higher compared to the recommendations of both the AAP (45 dB) and the Ministry of Health (averagely 50-55 dB per hour and 70 dB at maximum) (6,38). This shows the necessity of increasing interventions aimed at reducing noise, inspecting the environment and staff continuously, and planning interventions aimed at reducing noise both at the institutional level and by healthcare professionals and to rigorously apply these interventions. Many measures can be taken to reduce noise. These measures may include applying "quiet time" throughout the shift (26,31), reducing bedside visits, turning down the volume of monitors and alarms, taking phones out of the unit (39), speaking in a low voice (40), not dragging things in the unit, avoiding loud

Table II. Evaluation of weekday and weekend noise measurements with noise meters giving visual and auditory alarms and digital noise meter

	Group 1				**Group 2**				**Weekday (Group 1- Group 2)**		**Weekend (Group 1- Group 2)**	
	Weekday	**Weekend**	**¹t**	**p-value**	**Weekday**	**Weekend**	**¹t**	**p-value**	**²t**	**p-value**	**²t**	**p-value**
	M ± SD	**M ± SD**			**M ± SD**	**M ± SD**						
Week 1	69.07±1.11	69.46±2.40	-0.874	0.391	70.86±0.72	71.36±1.05	**-2,093**	**0.048***	**-6,607**	**0.001****	**-3,560**	**0.001****
Week 2	69.94±1.28	70.43±1.03	-1,451	0.160	70.43±1.31	70.07±0.86	1,590	0.126	-1,321	0.193	1,317	0.194
¹t	**-2,941**	-1,830			1,759	**5,000**						
p	**0.007****	0.080			0.092	**0.001****						

¹t: Paired Sample t-test, ²t: Student-t test, *p<0.05, **p<0.01
SD: Standard deviation

shoes (34), setting the ring tone of the phone to minimum (23) and using visual alarm systems (26-29).

In this study, a "noise meter emitting a visual and auditory alarm" was used to reduce the noise level. It is indicated that the most important property of these devices is that they are effective in reducing maximum noise levels. Reducing this condition which causes infants to experience sudden stress is an indicator of the effectiveness of these devices (29). Jousselme et al. (28) reported that the noise level was reduced to 2 dB as a result of using a noise meter emitting a visual alarm. It is recommended that noise meters emitting a visual alarm be used in NICUs, because they reduce noise levels by causing behavioural changes in healthcare professionals (27-29). In one study, it was reported that noise meters emitting a visual alarm reduced noise levels in the short term, but this decrease was not sustainable over one year even when a "quiet time" was added (26). Moreover, it has been emphasized that continuous education regarding the harmful effects of noise is very important for permanent noise reduction in NICUs. Also, this study assessed whether or not healthcare professionals were affected by these devices which emit visual and auditory alarms. Interventions were made to reduce noise and they reduced the ambient noise level.

The total noise level in the NICU over the two-week period was found to be significantly lower in group 1 than in group 2, which confirmed hypothesis 1 ($p<0.05$; Table II). AAP (6) and White (41) state that the hourly noise level in NICUs should not exceed 45 dBA. In the Communiqué Regarding the Implementation Procedures and Principles of Intensive Care Services in Bedded Health Facilities in Turkey, it is reported that NICUs should not exceed 50-55 dB per hour on average and 70 dB at maximum (38). However, it was observed that the noise levels are not at the desire level either in this study or in other studies.

When comparing the weekly noise levels of the two groups on weekdays and at the weekend, it was found that noise levels were significantly lower in group 1 than group 2 in week 1; whereas, in week 2, there was no difference between the groups. The decrease in the noise levels in week 1 in group 1 did not continue in week 2, which was thought to be associated with intensity of work in the NICU and uncontrollable individual and environmental factors such as changes of healthcare professionals, the impact of visitors and the noise levels of materials used. In addition, it was noted that the noise level in the present study was higher than the level found by Jousselme et al. (28), which might be associated with the fact that besides a visual alarm, the noise meter used in this study emitted an auditory alarm when the sound exceeded 70 dB. In addition, the first week may have caused a change in behaviour of the staff members due to the newness of the device in the unit, and in the second week, it was observed that there was no difference between the weekday and weekend noise levels in both groups, whereas it was expected that the noise level would decrease further in the second week. However, it was observed that there was no difference between the groups in terms of noise level in the 2nd week. This situation may have developed due to uncontrollable environmental factors (alarm sounds, mobile phones, emergency interventions and so on), the intensity of the service and the carelessness of the staff members working in the shift. In this case, besides the devices we use to reduce noise, training staff members on this issue and using these devices together with different initiatives can increase effectiveness.

In other studies, "noise meters emitting only a visual alarm" can be compared with "noise meters emitting both a visual and an auditory alarm" and their effectiveness can be evaluated.

It was seen that noise meters emitting a visual and auditory alarm are effective in reducing the ambient noise level; however, this decrease did not continue at the required level according to the levels specified. Therefore, it is crucial that instead of only one application, many applications should be conducted simultaneously in units to reduce noise and these applications should be converted into behavioural changes by healthcare professionals.

Conclusion

It was found that the total noise level in the NICU over a two-week period was significantly lower in group 1 than group 2.

According to these results, it can be suggested to;

Use a noise meter emitting a visual and auditory alarm in NICUs,

Measure noise regularly in NICUs in order to protect infants and staff members from possible problems caused by noise,

Create and apply regulations aimed at reducing noise in accordance with corporate standards.

Acknowledgements

The researchers thank the staff and families of the neonatal intensive care unit where the study was conducted. We thank Berkay Medical for the noise meter giving visual and auditory alarms and digital noise meters. This study was presented for poster presentation in 27th National Neonatology Congress between 3-7 April 2019.

Ethics

Ethics Committee Approval: Ethics committee approval (date: 11/29/2017; no: 488) from İstanbul Medipol University Ethics Committee as well as institutional permission were obtained for the study.

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.B., M.C.İ., A.T., Concept: S.B., M.C.İ., Design: S.B., M.C.İ., Data Collection or Processing: S.B., M.C.İ., A.T., Analysis or Interpretation: S.B., M.C.İ., Literature Search: S.B., M.C.İ., Writing: S.B., M.C.İ.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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J Pediatr Res 2021;8(4):462-8
DOI: 10.4274/jpr.galenos.2021.92477

Original Article

Prevalence of Medically Compromised Children Among Dental Patients: A 10-Year Retrospective Study

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ABSTRACT

Aim: Medical conditions can affect oral health status as well as directly affecting dental treatment planning and patient management. The purpose of this study is to evaluate the prevalence of various medical conditions of those children in a community-based dental hospital.

Materials and Methods: In this study, the anamnesis forms of 30,161 children aged 0-15 who were referred to a university dental hospital from a defined geographical area in southeastern Turkey between 2010 and 2020 were evaluated. Patients who had a medical risk and chronic/systemic/genetic diseases were included in this study. Those medical records for acute conditions, cooperation problems and isolated tooth anomalies not associated with any syndrome or genetic disease were excluded from this study.

Results: 1,619 (5.36%) of the patients included in the study had at least one systemic disease. According to the medical conditions which were examined and categorized, the most common disease group was neurological disorders (17.1%) and the most common disease was epilepsy (11.7%). It was followed by Congenital/chromosomal malformations (14.8%), while autism was the most common in this group with a rate of 36.7%.

Conclusion: Obtaining a detailed medical history of every patient who is referred to the dental clinic is very significant in terms of treatment planning, non-routine required protocols and complications. Dentists and pediatricians should evaluate more frequently and more rigidly, using a multidisciplinary approach, children with systemic diseases whose oral and dental health is at greater risk as a result of their medical condition.

Keywords: Chronic diseases, medical records, pediatric dentistry, medically compromised children, prevalence

Introduction

The human body is a whole which consists of organs and systems which affect each other. There is a direct or indirect relationship between systemic diseases and oral/dental health (1). Sometimes, a change in the oral cavity can be a manifestation of a systemic disease.

Furthermore, a medical condition can affect dental treatment planning, risks of complication occurrence, the drugs which can be prescribed, and the health of patients and dentists (2,3). Additionally, in the presence of certain diseases, bacteremia may occur due to dental infection or invasive dental procedures and it can pose serious risks such as endocarditis (3). Therefore, it is very important for dentists to obtain a detailed anamnesis record containing the past medical history of their patients giving their diseases, surgeries, and usage of medications (4).

***This manuscript was presented as an oral presentation in III. Prevent from Caries Symposium (Online/13-14 November 2020).**

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Received: *04.02.2021* **Accepted:** *09.04.2021*

In previous studies on the medical profiles of patients who were referred to dentists, it was observed that fewer systemic diseases were determined in pediatric patients compared to adults, and their common disease profiles differ from those of adults (5-7). It is remarkable that most of these studies on the prevalence of systemic diseases and medical records in dentistry focused on adult patients (5,8,9). Some systemic diseases can cause changes in the oral cavity. Even the first symptom may occur in oral tissues and the disease can be diagnosed by means of these symptoms. Therefore, dentists' detailed anamnesis records and detailed examinations can help to identify the underlying etiology of oral changes, and so enable early intervention (10). The aim of this study was to determine the prevalence of systemic diseases and medical profiles in pediatric patients referred to a dental clinic by means of a retrospective evaluation of 10 years' worth of patient records.

Materials and Methods

In this study, the medical records of 30,161 children aged 0-15 who had visited a university dental hospital between January 2010 and June 2020 were included in the evaluation. A detailed consent form is routinely obtained from all patients/parents who are refer to our clinic before their examination. In this form, it is stated that "medical/dental records and oral photographs can be used for diagnostic, scientific, educational or research purposes while keeping any identifying information of the patients confidential" and written consent of the parent is obtained. These consent forms are stored in the department archive. Therefore, an additional consent form was not created for this retrospective study.

The patients' medical records, which were created electronically by dentists, were analyzed. Children with a medically compromised condition or a chronic/systemic/genetic disease in their records were included in this study. Anamnesis records containing non-cooperation without mental retardation, acute conditions (trauma, extraoral dental abscess, etc.) and isolated dental anomalies which are not associated with any syndrome or genetic disease (gemination, fusion, turner hypoplasia, MIH, etc.) were excluded.

The medically compromised conditions were classified into 17 subgroups as follows: neurological disorders, congenital/chromosomal malformations, cardiac diseases, respiratory diseases, allergy, endocrine disorders, hematological diseases, mental retardation, psychiatric disorders, oncological diseases, autoimmune diseases, gastroenterological diseases, renal diseases, physical disabilities, dermatological diseases, metabolic diseases and others. FMF and celiac disease were included in the Autoimmune diseases and all cancers were collected in the Oncological diseases group. If a patient had more than one disease in the same group, the disease was recorded as singular. The data of the patients were collected and encoded by their category using a Microsoft Excel spreadsheet (Microsoft, Redmond, Washington, USA). The coded data were analyzed using SPSS (version 23.0; SPSS Inc., Chicago, Illinois, USA). The values obtained were calculated in terms of frequency and percentage. Pearson's chi-square test was applied to verify the association between the disease groups and the patients' age and gender, separately.

Results

1,619 (5.36%) of the 30,161 patients whose anamnesis forms were examined had at least one systemic disease or medical record that required attention. 60% of these 1,619 patients were male. In this study, the patients had an age range of 0-15 years with a mean age of 7.61±3.16 years (Figure 1).

1,852 systemic diseases/medical conditions were detected in 1,619 patients. 207 patients had more than one medical condition which belonged to different disease groups (Table I).

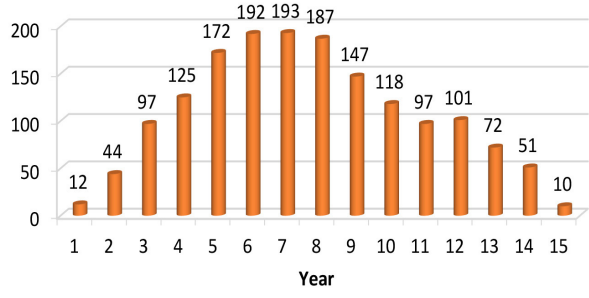

Figure 1. The age distribution of patients

Table I. Distribution of patients according to the number of diseases they have

Groups	N
Patients with 1 disease group	1,412
Patients with 2 disease group	182
Patients with 3 disease group	24
Patients with 4 disease group	1
Patients without disease group	28,542
Total	**30,161**

In the current study, the most prevalent medical condition was neurological disorders (17.1%), and the most common disease was determined to be epilepsy (11.6%). Congenital/chromosomal malformations (14.8%) were the second most common group, and autism constituted 36.7% of this group. The third most common disease group was cardiac diseases with a rate of 13.9%, followed by respiratory system diseases with a rate of 13.4% (Table II). The comparison of the prevalence of diseases by age groups is given in Table II. The prevalence of cardiac diseases between 0-5 years of age was statistically significantly higher than 5-10 years. Hematological diseases and Congenital/chromosomal malformations were significantly higher in the 0-5 age group than in the 10-15 age group.

Asthma accounted for 85.1% of this group, and was the second most common disease among all diseases with 11.4% (Table II and Figure 2). The 5 most common diseases are given in Figure 2.

Table II: Disease categories and frequencies

Medical condition	Type of disease	Age group						n	%
		0-5 y		5-10 y		10-15 y			
		n	%	n	%	n	%		
Neurological disorders	Epilepsy, CP, hydrocephaly...	87[a]	16.4%	166[a]	17.5%	64[a]	17.2%	317	17.1
Congenital/chromosomal malformations	Autism, Down syndrome, apert synd., ectodermal dysplasia...	**94[a*]**	17.8%	138[a,b]	14.5%	**43[b*]**	11.6%	275	14.8
Cardiac diseases	Congenital/acquired heart diseases and surgeries	**89[a*]**	16.8%	**115[b*]**	12.1%	54[a,b]	14.5%	258	13.9
Respiratory diseases	Asthma, bronchitis, dyspnea...	68[a]	12.9%	130[a]	13.7%	51[a]	13.7%	249	13.4
Allergy	Drug and food allergies...	36[a]	6.8%	81[a]	8.5%	29[a]	7.8%	146	7.8
Endocrine disorders	Diabetes mellitus, hypothyroidism, rickets...	29[a]	5.5%	65[a]	6.8%	23[a]	6.2%	117	6.3
Hematological diseases	Anemia, hemophilia, thalassemia...	**35[a*]**	6.6%	48[a,b]	5%	**11[b*]**	3%	94	5
Mental retardation	Isolated mental retardation without a diagnosed disease	**11[a*]**	2.1%	27[a,b]	2.8%	**19[b*]**	5.1%	57	3
Psychiatric disorders	Attention deficit disorder, hyperactivity, anxiety...	12[a]	2.3%	29[a]	3%	16[a]	4.3%	57	3
Oncological diseases	Type of leukemias, neuroblastoma...	10[a]	1.9%	30[a]	3.2%	13[a]	3.5%	53	2.8
Autoimmune diseases	Immune deficiency, FMF, celiac disease...	**8[a*]**	1.5%	25[a,b]	2.6%	**17[b*]**	4.6%	50	2.6
Gastroenterological diseases	Gastric and liver diseases	14[a]	2.6%	20[a]	2.1%	5[a]	1.3%	39	2.1
Renal diseases	Kidney failure, kidney transplantation...	10[a]	1.9%	21[a]	2.2%	5[a]	1.3%	36	1.9
Physical disabilities	Blind, deaf and mute...	9[a]	1.7%	15[a]	1.6%	6[a]	1.6%	30	1.6
Dermatological diseases	Urticaria, epidermolysis bullosa...	**0[a*]**	0%	11[b]	1.2%	5[b]	1.3%	16	0.8
Metabolic diseases	Phenylketonuria, mucopolysaccharidosis...	6[a]	1.1%	5[a]	0.5%	3[a]	0.8%	14	0.7
Others	Vomiting reflex, zinc deficiency...	11[a]	2.1%	25[a]	2.6%	8[a]	2.2%	44	2.3
Total		529	100%	951	100%	372	100%	1852	100%

Age groups with the same letter mean "no significant difference", while age groups with different letters mean "there is a significant difference" (*p<0.01).
CP: Cerebral palsy, FMF: Familial Mediterranean Fever, y: Year

When patients with mental or physical disabilities were collected in a special category, it was determined that autism was the most common medical condition among these patients (28.1%). Autism was followed by cerebral palsy, Down's syndrome and mental retardation not associated with any syndrome (Figure 3). The rate of mental or physical disabilities among all diseases was determined to be 19.4%.

The gender distribution of medically compromised dental patients is given in Table III. Respiratory diseases had significantly higher prevalence in male patients than in female patients. Endocrine disorders were found to be significantly more common in female patients than in male patients (Table III).

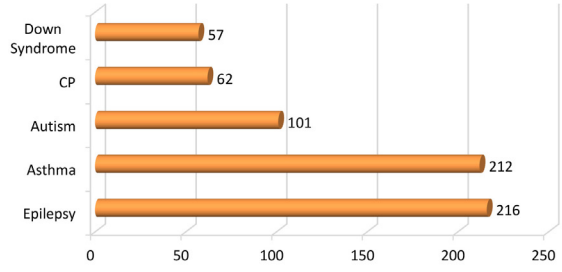

Figure 2. Most frequent diseases

One hundred and ninety-four (11.98%) of the 1,619 patients were treated under general anesthesia. These patients mostly had congenital or chromosomal malformations (34.2%). This was followed by neurological disorders (23.9%), cardiac diseases (10.7%) and isolated mental retardation (9.5%), respectively.

Discussion

Oral care is part of parental responsibility in medically compromised children (MCC), as in all children aged 0-6 years. However, after the age of 6 years, the child, who needs to gradually take an active role in his/her self-care, may be passive due to common psychosocial and educational

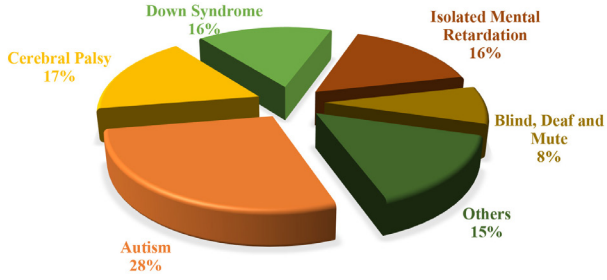

Figure 3. Mental or physical disabilities

Table III. Gender distribution of medically compromised dental patients

Medically compromised condition	Number of female/male	Frequency of female/male (%)	Chi-square for gender difference (p-value)*
Neurological disorders	130 : 187	20.1% : 19.3	0.635
Congenital/chromosomal malformations	99 : 176	15.3% : 18.1	0.114
Cardiac diseases	114 : 144	17.6% : 14.8	0.137
Respiratory diseases	78 : 171	12.0% : 17.6	0.002*
Allergy	67 : 79	10.3% : 8.1	0.129
Endocrine disorders	60 : 57	9.3% : 5.9	0.010*
Hematological diseases	36 : 58	5.6% : 6.0	0.725
Mental retardation	23 : 33	3.5% : 3.4	0.871
Psychiatric disorders	18 : 39	2.8% : 4.0	0.185
Oncological diseases	21 : 32	3.2% : 3.3	0.952
Autoimmune diseases	24 : 26	3.7% : 2.7	0.242
Gastroenterological diseases	18 : 20	2.8% : 2.1	0.350
Renal diseases	13 : 24	2.0% : 2.5	0.539
Physical disabilities	14 : 16	2.2% : 1.6	0.454
Dermatological diseases	6 : 10	0.9% : 1.0	0.836
Metabolic diseases	4 : 10	0.6% : 1.0	0.380
Others	12 : 32	1.9% : 3.3	0.080

*p<0.05

secondary handicaps caused by their medical condition (11). Additionally, parents focus more heavily on the follow-up and care of the chronic disease. Chronic diseases can lead to negligence on behalf of the parents with regard to oral/dental health and thus, these issues can be ignored until dental problems become acute (11,12). However, the body is a whole and one malfunction can affect the whole systems. Aggarwal's (6) "The dentist does not treat 'teeth in patients' but 'patients who have teeth'." statement supports the importance of this study. Therefore, dentists should obtain detailed information about the medical conditions of their patients and have knowledge about an appropriate treatment approach in light of their disease.

In previous epidemiological studies conducted in the general pediatric population, the prevalence of MCC was reported to be between 1.06% and 44% (13-15). In studies analyzing the medical profiles of patients visiting dentists, there were few prevalence studies focusing on pediatric patients, as there were more medical conditions in adults compared to children. Brown reported 211 of 386 patients were MCC (54.66%) in his study in 2009 (7). However, it was stated by the author that the hospital provides services to patients, 50% of whom are MCC requiring specialist care. In another study conducted on the pediatric population, the "report sensitivity" of the families was examined and it was determined that the MCC prevalence was 66% since the sample was mostly chosen from MCC (16). In the current study, the prevalence of MCC was 5.46%, which is considerably lower than the dentistry studies in the literature. However, it is consistent with studies conducted in the general pediatric population. It is clear that this important difference is related to the inclusion criteria of the studies. In addition, this difference can be explained by the different sample sizes, ethnic/socio-demographic reasons, and misreporting. Schwarz et al. (16), in their study comparing medical records with dental records, found that the sensitivity rate varied between 16% and 100% according to the disease groups (16). One reason for the low prevalence in this study may be misreporting.

In the current study, the higher incidence of medical conditions in males (60%) was found to be consistent with studies in pediatric patients in the literature (7,11,17). However, the prevalence of women was higher in studies conducted on adults (5,6,9).

In this study, neurological disorders were the most common disease group (17%). Although there are studies with the high rates of neurological disorders in the literature (11,16), it is difficult to certainly compare these findings because different categorizations and definitions are used in many studies. Since the number of studies on pediatric patients who were referred to dentists in the literature is limited, more studies are needed to get a clearer idea about prevalence. According to this study, epilepsy, which affects 7 out of every 1,000 children, is the most common disease in pediatric dental patients. Seizures in epileptic children can cause soft tissue injuries, facial fractures, dental trauma, and TMJ disorders. Furthermore, one of the most common reasons of gingival hypertrophy is phenytoin which is an antiepileptic drug (18). Therefore, dentists should inquire about the drugs used by their patients as well as the medical conditions of their patients. In patients who have oral manifestations, pediatric neurology should be consulted and a modification/change of medication should be requested. These patients should be followed up with a multidisciplinary approach.

Congenital/chromosomal malformations were the second most prevalent group among all (14.8%). The frequency of consanguineous marriages in the region where the study was conducted may have affected this result. It has been reported that consanguineous marriages increase the risk of various multifactorial diseases, mental retardation, developmental disorders, congenital, neurological and chromosomal malformations (19).

Of the 258 heart diseases detected in this study, 104 were congenital, 36 were acquired, and the rest were of unknown cause. The incidence of heart disease in children aged 0-5 years was significantly higher in this sample compared to the 5 to 10-year-old group ($p<0.01$). The reason for this may be that congenital heart diseases were detected more in this study. Nevertheless, no statistically significant difference was found when children aged 0-5 years and 10-15 years were compared. Acquired heart diseases is more prevalent in older children (20). This may explain the increased rate of heart disease in children aged 10-15 years. From the dentist's perspective, infective endocarditis, which carries a high risk of mortality, is the most important risk to consider in these patients. There is strong evidence that untreated dental/periodontal diseases and some invasive treatments are an important etiological factor for endocarditis (21). The ideal dental care approach in high-risk patients is for them to receive preventive dental care before dental problems occur, and to follow a prophylactic antibiotic procedure during the treatment phase (21). Preventive dental care applications include procedures such as performing routine check-ups more frequently and re-mineralizing early caries lesions before cavitation. In addition, increasing routine check-ups makes it possible to detect and treat risky teeth that may be

the source of focal infection. Both dentists and pediatricians should take extra care with a multidisciplinary approach to oral health in children with heart disease.

In this study, mental and physical disabilities are evaluated in Figure 3 as a special subgroup of medical conditions in terms of having unique difficulties in dental care and treatments. Children with disabilities have poorer oral health and more unmet dental treatment. The underlying causes may be barriers to access dental services, poor oral hygiene, and disability-related factors (22).

Unlike respiratory diseases, which were statistically significantly higher in males, endocrine disorders were more prevalent in females. The gender distribution in the two disease groups in our study is also consistent with some adult studies (5,6). In this study, asthma which accounts for 85.1% of respiratory diseases, is significantly more common in males, which is consistent with the literature. Asthma and drugs such as inhaled corticosteroids used in its treatment have been blamed for increasing the prevalence of dental caries, causing erosion and periodontal problems in many studies (23). The dentist should consider these risks, and evaluate the patient within the scope of preventive treatment.

Study Limitations

Within the limits of this study; some information may be incomplete due to its retrospective nature. The standardization of the information may have been affected since it covers a long period and therefore data was not recorded by a single dentist. These problems encountered due to the design of retrospective studies could not be minimized as more detailed information about medical conditions could not be evaluated within the scope of the study. The lack of specific records on the American Society of Anesthesiologists classification or medications in most patients resulted in not being able to collect data on this issue. Another problem with categorizing medical information was that some diagnoses did not belong to an existing category. This information was collected in the "others" category in order not to increase the possible relative agreement between records incorrectly. This category accounted for only 2.3% of all medical conditions (n=1,852). Creating 17 disease groups in the study was also a factor designed to reduce this rate.

Conclusion

Although the prevalence of medical conditions in children is much lower than in adults, sometimes this information can be crucial. Preventive dentistry practices are very important in all children, but these practices should be applied more frequently and rigidly in children whose oral and dental health is compromised as a result of their medical condition. The types of medical conditions and how often they are detected in pediatric patients who are referred to the dentist is valuable data as it allows dentists to review this information so that they can plan, treat and manage complications with regards to dental health services. Dentists and pediatricians should collaborate in a multidisciplinary approach in MCC.

Ethics

Ethics Committee Approval: Ethics committee approval for the study was obtained from the Non-Interventional Clinical Research Ethics Committee of the İnönü University (number: 2020/1075).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Data Collection or Processing: Ş.N.Ö., Analysis or Interpretation: Ş.N.Ö., Writing: P.D., Ş.N.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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J Pediatr Res 2021;8(4):469-78
DOI: 10.4274/jpr.galenos.2021.99266

Original Article

Evaluation of the Effectiveness of Reproductive Health Education Program Given to Adolescents

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ABSTRACT

Aim: This study aimed to determine the effectiveness of reproductive health education for adolescents.

Materials and Methods: We used a quasi-experimental design with pre-test and post-test control groups. A total of 161 adolescents were included in this study, 84 in the intervention group and 77 in the control group. A personal information form and a reproductive health information form were used for data collection. Reproductive health training was given in classes of 2 hours a week (total 14 hours) by the researchers. Before the intervention and 2 months after the intervention, the knowledge level of the students was evaluated using data collection forms.

Results: There was no statistically significant difference ($p>0.05$) between the mean pre-test knowledge scores of the intervention and control groups (17.97±5.22 and 18.18±5.28, respectively). A statistically significant difference was found between the intervention and control groups' mean post-test scores (27.51±3.83 and 18.36±5.88, respectively) ($p<0.05$).

Conclusion: Students who participated in the reproductive health education program had a higher mean knowledge score for reproductive health after the program, which shows that this reproductive health education program is effective.

Keywords: Adolescent, reproductive health, health education, adolescent health

Introduction

Adolescence is a period defined as the transition from childhood to adulthood, where various physiological and anatomical changes take place (1,2). According to the World Health Organization (WHO), people in the age group of 10-19, which corresponds to approximately 1.2 billion people worldwide, are defined as adolescents (3). Adolescents (aged 10-19 years) represent approximately 16% of the Turkish population (4). Although it is considered a healthy time of life during which new options and ideas are explored, it is also a vulnerable period of life where sexual identity and self-esteem are developed, and risky behaviors may emerge in terms of reproductive and sexual health (5,6).

The age at sexual activity initiation is gradually decreasing around the world, and it is known that sexual activity is widespread during adolescence (7,8). In Turkey, the first sexual experiences occur, although at a low rate, among those aged 13 years or even younger, although mostly between the ages of 14-15 years (9,10). Previous studies reported that 21.9% of adolescent girls and 38.7% of adolescent boys in the USA have their first sexual experiences at the age of 14 years or even younger (11) and that 13.33% of adolescents in southwest Ethiopia have their first experiences under the age of 10 years, 20% between the ages of 10 and 14 years, and 66.67% between the ages of 15 and 19 years (12).

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Received: *23.02.2021* **Accepted:** *30.04.2021*

Teaching a child to be sexually responsible is an important part of sex education (13). However, in Turkey- and worldwide-there are concerns that education about reproductive health and sex may increase the curiosity of adolescents about sexuality and encourage them to become sexually active at an earlier age (14). Previous studies have shown that adolescents whose parents perceive information about reproductive and sexual health as a taboo or shameful topic obtain their information from unofficial sources and thus are left with negative or insufficient knowledge compared to their peers (13-21).

Most countries have policies or strategies that support comprehensive reproductive health and sexual education; however, very few of these countries have implemented and maintained these programs (22). The European Commission and the Ministry of Health (MH) of the Republic of Turkey conducted a "Reproductive Health Program" between 2003 and 2007 with five intervention fields, one of which was the reproductive health of adolescents (23), but this and similar programs were not continued. To meet the informational needs of adolescents concerning reproductive health and sex education, the health and education sectors must work together (24). Based on the results of studies conducted by the WHO on comprehensive reproductive health and sexual education programs included in the curricula in schools, it has been reported that reproductive health and sex education programs actually lead to a delayed initiation of sexual intercourse and decreases in the frequency of intercourse, the number of sex partners and risk taking, and also leads to an increase in the use of condoms and other contraception methods (22). In this context, middle-school children should be provided with a comprehensive reproductive and sexual health education program, including information on the anatomy of the reproductive organs, pregnancy avoidance, and protection against sexually transmitted diseases (2). The literature states that most adolescents prefer classes on reproductive and sexual health education in school (16,25-27) and that they wished that they had counsellors on reproductive and sexual health at schools or in health institutions (26,28).

In the study by Minguez et al. (29), it was observed that students who had access to comprehensive reproductive health services in school health centers engaged in reproductive health education and counselling and more frequently used hormonal contraception. Another study in Nigeria reported that the sex education of adolescents was effective in that the intervention group showed fewer risky sexual behaviors than the control group (2).

There have been studies conducted in Turkey with university students on reproductive health and sexual health education (19,30-32), and studies in the literature have been conducted with adolescents about sexual health education (17,33,34) and reproductive health (6,35-44). However, the number of studies examining the effectiveness of sexual health (33,34) and reproductive health education (41) provided for adolescents between the ages of 11 and 14 years is limited.

School nurses play an important role as members of the school health team by providing education on reproductive health and sexual health at schools around the world (45). Although not all schools in Turkey have a school nurse yet, the MH has issued the Regulation on the Amendment of Nursing Regulation regarding the duties, powers, and responsibilities of school nurses in terms of school health. It states that the education provided by the school nurse includes reproductive health and sexual health education (46). The present study, one of the few investigating the efficacy of reproductive health education for Turkish adolescents, is the first to investigate the effectiveness of reproductive health education for adolescents in Kütahya, which is located in the inner Aegean region of Turkey. It is proposed that this study will form the basis for future studies on improving reproductive health in adolescents.

This study was conducted to determine the efficacy of the reproductive health education program given to adolescents.

The hypotheses of the study were:

Hypothesis 1: The intervention group's mean post-test knowledge score will be higher than their mean pre-test knowledge score.

Hypothesis 2: The intervention group's mean post-test knowledge score will be higher than the control group's mean post-test knowledge.

Materials and Methods

Study Design and Participants

This study used a quasi-experimental design with pre-test and post-test control groups. The research was conducted in a single center. The study population consisted of 196 students aged 11 to 14 years who attended secondary school in Kütahya between March 2017 and July 2017.

This school is one of the schools that represents the general socio-demographic characteristics of Kütahya, and it has the largest student population. Power analysis was done with the G*Power program. The sample size was

calculated by using the effect size in the sample size calculation. The total sample size was determined to be 128 in calculations based on a type I error rate of 5%, a medium effect size of 0.25 and a power ratio of 80%. Considering data losses, 130 students were planned to be included in the sample. However, 84 students were included in the intervention group and 77 students in the control group in the study. No blinding process was used in the data collection process of the study. There were a total of 6 mixed classes in the school. The classes were selected by a simple random sampling method (coin toss) and assigned to either the control or intervention group. In this way, the control group was comprised of 3 classes and the intervention group was comprised of 3 classes. The students in these classrooms who volunteered to participate in the study formed the sample of the study. In this way, students were prevented from getting information about education from each other. The data were collected in the classroom environment at the school, and training sessions were held at hours deemed appropriate by the school. The training hours and the training area are determined by the school directorate.

The inclusion criteria were being between 11 and 14 years old, having reading and writing literacy, and parental and student verbal and written consent. Students' participation was voluntary.

Data Collection

Measurements

The study data were collected using a personal information form and a reproductive health information form. Expert opinion was sought in the preparation of the reproductive health information form. In addition, the adolescents in the intervention group were provided with training using a booklet entitled "Reproductive Health" prepared by the researchers based on the literature and expert opinions. After obtaining expert opinion, the final form of the data collection form and training booklet was given.

The data collection tools were examined by the Kütahya Provincial Directorate of National Education Guidance Research Center for their suitability for the students of that age group and in terms of clarity. After this examination, they were deemed to be appropriate.

Personal information form: the personal information form consisted of questions about the socio-demographic characteristics (age, gender, family type, economic situation, etc.) and the reproductive health knowledge of the adolescents and the socio-demographic characteristics of the parents (educational status, marital status, etc.).

Reproductive health information form: this form was designed by the researchers following a literature review and was evaluated by an expert (7,19,32,47,48). The reproductive health information form consisted of 33 questions measuring the level of knowledge regarding changes in the adolescent period, reproductive health and reproductive rights of adolescents, sexually transmitted diseases, anatomy and physiology of the male and female reproductive systems, and risky acts of behavior. One point was awarded for each correct answer and 0 points were awarded for each incorrect answer on the reproductive health information form. The lowest possible score was 0, and the highest possible score was 33.

Higher scores on the reproductive health information form indicated that the reproductive health knowledge levels of the adolescents were increasing.

Intervention

The intervention group: the adolescents included in the intervention group were first asked to complete the personal information form and the reproductive health information form as a preliminary test. Next, they participated in a reproductive health education program for a total of 14 hours (2 hours per week for 7 weeks). In this program, girls and boys were educated by the researcher in separate groups.

In the training given to the adolescents within the scope of the reproductive health education program, reproductive health education booklets and a PowerPoint presentation based on the booklets were used (40,19,47). Additionally, models were shown while explaining the anatomy of the reproductive organs.

Six weeks after the training was provided by the researcher within the scope of the reproductive health training program, the adolescents in the intervention group were asked to complete the reproductive health information form for a second time in a classroom environment at the school (Table I).

The control group: two forms, the personal information form and the reproductive health information form (in the form of a pre-test), were completed by those adolescents in the control group. No intervention was made for the control group other than the normal procedures during this process.

The reproductive health information form was administered six weeks later as a post-test. Educating the

Table I. Reproductive health education program for adolescents in Kütahya, Turkey

Week	Education module	Education time
1st	Introduction, meeting the students	2 hours
2nd	Adolescent period, changes in the adolescent period	
3rd	Reproductive system anatomy and physiology	
4th	Risky behavior in the adolescent period	
5th	Sexually transmitted diseases and prevention	
6th	Reproductive health, reproductive rights	
7th	Closing, general evaluation	

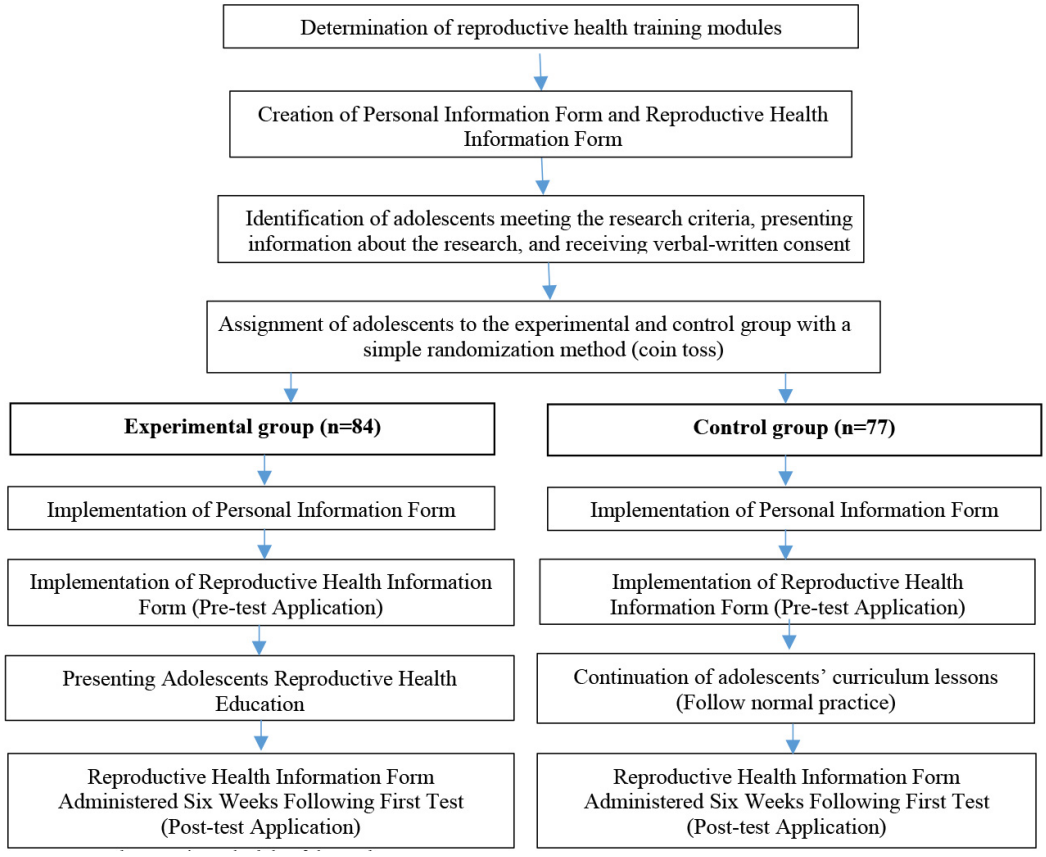

Figure 1. Implementation schedule of the study

intervention group but not providing education for the control group creates an ethical problem. Therefore, the control group received reproductive health education after they completed the post-test (Figure 1).

The purpose of the study was explained to each student and their family, and joint consent was obtained. Ethical approval for the study was obtained from the Ethics Committee of the Non-Interventional Clinical Investigations Eskişehir Osmangazi University (IRB no. 2017-07). The Directorate of National Education of Kütahya issued a research permit (dated on 05.04.2016, numbered 53490996-44-E.3831220).

Statistical Analysis

All analyses were performed using the Statistical Package for Social Sciences (SPSS) program, version 20. Shapiro-Wilk test was used to examine the distribution of the data and it was observed that the data were distributed normally. Therefore, parametric tests were used in the analysis of the data. Numbers (n), percentages (%), chi-square analyses

(X^2) and t-tests for dependent and independent groups were used during the data analysis (49). Chi-square test was used to examine the difference between intervention and experimental group characteristics. The t-test was used to evaluate the knowledge levels of the students in the intervention and control groups before and after the education. The level of statistical significance was accepted as α=0.05.

Results

The adolescents' mean age was 12.83±0.47 years in the control group and 12.80±0.54 years in the intervention group. Whereas there was no statistically significant difference between the groups in terms of age, gender, number of siblings, area of longest residence, health insurance, current residence, and family type (p>0.05), there was a statistically significant difference in the income level of the adolescents' families (p<0.05; Table II).

There was no statistically significant difference between the intervention and control groups in terms of maternal education level, mother's working status, or parental marital status (p>0.05); however, there was a statistically significant difference between the groups in terms of the father's education level and father's occupation (p<0.05; Table III).

There was no statistically significant difference between the intervention and control groups in terms of hearing about the reproductive health concept, reproductive health knowledge level, or receipt of reproductive health education at school in the past (p>0.05; Table IV).

The mean pre-test reproductive health information score of the adolescents in the intervention group was 17.97±5.22, and the mean pre-test score of the adolescents in the control group was 18.18±5.28. There was no statistically significant difference between the mean pre-test scores of the adolescents in the intervention and control groups (p>0.05; Table V).

The mean post-test reproductive health information score of the adolescents in the intervention group was 27.51±3.83, and the mean post-test score of the adolescents in the control group was 18.36±5.88. There was a statistically significant difference between the mean post-test scores of the adolescents in the intervention and control groups (p<0.05; Table V).

In-group comparisons of the intervention and control groups related to reproductive health information pre-test

Table II. Comparison of socio-demographic characteristics of adolescents in Kütahya, Turkey

Characteristics	**Control**	**Intervention**		
Age	**Mean ± SD**	**Mean ± SD**	**t**	**p-value**
	12.83±0.47	12.80±0.54	0.268	0.789
	n (%)	**n (%)**	**X^2**	**p**
Gender				
Female	43 (49.4)	44 (50.6)	0.194	0.660
Male	34 (45.9)	40 (54.1)		
Number of siblings				
1	12 (48.0)	13 (52.0)	0.238	0.888
2	42 (49.4)	43 (50.6)		
3 and more	23 (45.1)	28 (54.9)		
Area of longest residence				
City	68 (47.2)	76 (52.8)	0.199	0.655
Rural area	9 (52.9)	8 (47.1)		
Health insurance				
Yes	73 (47.1)	82 (52.9)	0.887	0.427
No	4 (66.7)	2 (33.3)		
Current residence				
Home/Family	74 (49.0)	77 (51.0)	1,358	0.244
Dormitory/ Housing	3 (30.0)	7 (70.0)		
Family type				
Immediate family	64 (47.4)	71 (52.6)	0.927	0.629
Extended family	11 (55.0)	9 (45.0)		
Broken family	2 (33.3)	4 (66.7)		
Income status				
Income exceeds expenses	19 (32.8)	39 (67.2)	13,585	**0.001**
Income equal to expenses	55 (60.4)	36 (39.6)		
Income is less than expenses	3 (25.0)	9 (75.0)		

SD: Standard deviation

and post-test score averages were examined. The mean pre-test and post-test scores of the intervention group were 17.97±5.22 and 27.51±3.83, respectively. The difference between the mean pre-test and post-test scores of the intervention group was found to be statistically significant (p<0.05; Table V). The mean pre-test and post-test scores of the control group were 18.18±5.28 and 18.36±5.88, respectively. There was no statistically significant difference between the mean pre-test and post-test scores of the control group (p>0.05; Table V).

Table III. Comparison of the characteristics of the adolescents' families in Kütahya, Turkey

Characteristics	Control	Intervention		
	n (%)	n (%)	X^2	p-value
Mother's education level				
Primary school	40 (43.5)	52 (56.5)	2,617	0.270
High school	29 (50.9)	28 (49.1)		
University and above	8 (66.7)	4 (33.3)		
Father's education level				
Primary school	12 (38.7)	19 (61.3)	6,044	**0.049**
High school	47 (57.3)	35 (42.7)		
University and above	18 (37.5)	30 (62.5)		
Mother's employment status				
Employed	22 (48.9)	23 (51.1)	0.028	0.866
Unemployed	55 (47.4)	61 (52.6)		
Father's occupation				
Laborer	40 (62.5)	24 (37.5)	10,038	**0.018**
Civil Servant	18 (34.6)	34 (65.4)		
Self-employed	14 (40.0)	21 (60.0)		
Retired	5 (50.0)	5 (50.0)		
Marital status				
Married	68 (45.9)	80 (54.1)	2,597	0.148
Divorced	9 (69.2)	4 (30.8)		

Discussion

It is thought that including reproductive health education in school curricula in developing countries will increase adolescents' reproductive health knowledge and decrease reproductive health problems. In this study, the efficacy of the "Reproductive Health Education Program" in increasing reproductive health knowledge among adolescents was evaluated.

It was determined that the adolescents in the intervention and control groups were similar in terms of age, gender, number of siblings, place of residence, health insurance status, and family type (p>0.05) but different regarding economic status (p<0.05; Table II). It is important for the reliability of the study that the characteristics of the students in the experimental and control groups are similar.

Table IV. Adolescents' views on reproductive health and reproductive health education in Kütahya, Turkey

Characteristic	Control	Intervention		
	n (%)	n (%)	X^2	p-value
Heard the concept of reproductive health				
Yes	41 (47.1)	46 (52.9)	0.037	0.875
No	36 (48.6)	38 (51.4)		
Knowledge status on reproductive health				
Sufficient	26 (43.3)	34 (56.7)	0.774	0.379
Insufficient	51 (50.5)	50 (49.5)		
Obtained reproductive health education at school in the past				
Yes	17 (44.7)	21 (55.3)	0.190	0.663
No	60 (48.8)	63 (51.2)		

Table V. Comparison of reproductive health pre-test and post-test score averages

Characteristics	Control	Intervention	t	p-value
	Mean ± SD	Mean ± SD		
Pre-test score average	18.18±5.28	17.97±5.22	0.248	0.804
Post-test score average	18.36±5.88	27.51±3.83	-11,579	**<0.001**
	t= -0.338	t= -18,537		
	p=0.737	**p<0.001**		

SD: Standard deviation

In the current study, it was determined that the adolescents in the intervention and control groups were similar in terms of the mother's education level, working status, and marital status ($p>0.05$). However, they differed regarding the father's education level and occupation ($p<0.05$; Table III). Golbasi and Taskin (42) also reported in their study that the adolescents in the intervention and control groups were similar in terms of the mother's educational level, working status, and family type but differed regarding the father's educational level. In this study, it was observed that the group characteristics were different from each other in terms of the father's education level and occupation. Students studying in the province where the study was conducted can live in villages and towns near the city. It is thought that the different cultural and family structure of the students coming from the villages and towns near the city, the access to education and the different workforce preferences may be the cause of this difference.

In the current study, it was observed that adolescents were similar in terms of hearing about the concept of reproductive health, having knowledge about reproductive health, and having received reproductive health education at school in the past ($p>0.05$; Table IV). Handayani et al. (35) determined in their study that adolescents in the intervention and control groups were not similar in terms of having knowledge about reproductive health.

For reproductive health, the mean pre-test scores of the adolescents in the intervention and control groups were similar ($p>0.05$), and it was observed that the mean post-test score of the intervention group was higher than that of the control group ($p<0.05$; Table V). These results showed that the knowledge level of adolescents who received reproductive health education was higher than that of adolescents who did not receive education on this issue (control group). Previous studies also reported that the reproductive health level of knowledge of the intervention group who received reproductive health education was higher than that of the control group (7,31,37,42).

Previous studies examining the mean pre- and post-education reproductive and sexual health knowledge levels of adolescents reported that these knowledge levels were higher post education (36,41,43). In addition, it has been stated that the implemented reproductive health education program improved knowledge and behavior about sexuality and decision making for both girls and boys (41). Other previous studies on this subject reported that their reproductive health knowledge level of adolescent through post education was higher than that before education (39,44).

Parwej et al. (6) reported that after training was given for reproductive health, adolescents in a conventional education group and a peer education group had significantly higher reproductive health knowledge scores than adolescents in the control group. It was also determined that the post-education reproductive health knowledge scores in the conventional education group were similar to those in the peer education group.

A study that investigated the effects of peer education on adolescents' reproductive health knowledge reported that the knowledge level regarding reproductive health of adolescents in the intervention group was higher than that of adolescents in the control group (40). In another study that investigated the effects of a sex education program on adolescents, a statistically significant increase in adolescents' knowledge levels regarding changes during adolescence was found (17).

The intragroup comparisons of both groups (intervention versus control) showed that the mean post-test reproductive health knowledge score was higher than the mean pre-test score of the intervention group ($p<0.05$) and that the mean pre-test and post-test scores of the control group were similar ($p>0.05$; Table V). The results of the current study were similar to those of previous studies (7,31,37). Taylor et al. (50) stated in their study that reproductive health education applied to adolescents can be effective in preventing sexually transmitted diseases and unwanted pregnancies and increases their knowledge about reproductive health. de Castro et al. (51) reported that sexual health education for adolescents is effective in developing knowledge and attitudes about sexual and reproductive health and creating a positive effect on individuals' behaviors. When the relevant literature is examined, it is seen that reproductive health training for adolescents and young people is extremely effective. Young people are a high-risk group in terms of reproductive and sexual health, and it is extremely important that they can benefit from holistic, comprehensive reproductive health education. There are no standardized reproductive health training programs for adolescents in our country. Due to the family and cultural structure of our country, adolescents may face various obstacles such as inability to access services, embarrassment, stigma, lack of tolerance, negative attitudes and behaviors when faced with a problem related to reproductive and sexual health or when they are asked to obtain information. Due to various obstacles, adolescents

access information about reproductive health through informal means (media, internet, friends, etc.). The rapid socio-cultural change experienced makes adolescents who have not received adequate training in reproductive health during adolescence open to risks in sexual and reproductive health issues. For this reason, it is necessary to organize comprehensive training programs in order to prevent risky sexual behaviors, unwanted pregnancies, and/or sexually transmitted infections, which can be seen due to the lack of knowledge of adolescents, and ultimately to ensure that adolescents are safe in terms of reproductive health. The literature consistently shows the benefits of reproductive health education. This is in alignment with the present study, which illustrated that reproductive health education programs provided to adolescents are effective. Education programs that increase adolescents' reproductive health knowledge level in detail during secondary education may be effective in improving their reproductive health.

Study Limitations

From a country where data are limited (Turkey), the effectiveness of the implemented reproductive health education for adolescents is expected to provide an important contribution to the literature. Although the contribution of the study is important, there are limitations. In this study, randomization could not be done by sample selection. The study was conducted at a single center in Turkey. Since the city where the study was conducted does not represent the whole country, generalizations cannot be made. Due to the short duration of the educational program (limited to seven weeks), the long-term impact of the program and its sustainability could not be assessed. For this reason, long-term evaluation studies are necessary. In addition, due to the traditional structure of Turkish society, it is thought that students will be able to reach the right information about reproductive health by means of education program process and answering the questionnaire questions.

Conclusion

This reproductive health education program effectively created positive changes and attitudes in terms of the knowledge of reproductive health among secondary school students. As the study findings reveal, there was a significant increase in the adolescents' knowledge level after the training. Interventions that increase knowledge of reproductive health provide protection and improve adolescents' reproductive health. A widespread adoption of reproductive health education programs in schools is crucial to prevent risky behaviors. It is recommended that secondary school education curricula include reproductive and sexual health education.

Ethics

Ethics Committee Approval: Ethical approval for the study was acquired from the Ethics Committee of the Non-Interventional Clinical Investigations Eskişehir Osmangazi University (IRB no. 2017-07).

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Design: F.B., H.Y.S., Data Collection or Processing: F.B., H.Y.S., Analysis or Interpretation: F.B., B.Y., H.Y.S., Writing: F.B., B.Y., H.Y.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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J Pediatr Res 2021;8(4):479-84
DOI: 10.4274/jpr.galenos.2021.79446

Original Article

Risk Factors of Hyponatremia in Children with Lower Respiratory Tract Infection (LRTI)

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ABSTRACT

Aim: Lower respiratory tract infection (LRTI) is a serious illness especially in children under 5 years of age. Hyponatremia is the most common electrolyte abnormality seen in hospitalized children. This study aimed to evaluate the correlation between hyponatremia in children admitted to a paediatric ward, in the setting of acute LRTI in different age groups and to determine the association of hyponatremia with different types of acute LRTI in children.

Materials and Methods: This study included 231 clinically diagnosed children (1 month to 12 years) with acute LRTI. General examinations and systemic examinations were performed. Laboratory investigations included serum electrolyte level (Na+) and radiological investigations included chest X-ray. The conditions observed in the children included bronchopneumonia (BPN), lobar pneumonia, wheeze-associated LRTI (WALRI), bronchiolitis, and empyema. Statistical analysis was carried out using SPSS 16.0 version. A p-value <0.05 was considered statistically significant.

Results: Out of 231 cases, hyponatremia was present in 136 cases (58.9%). Mild, moderate, and severe hyponatremia were present in 83.8%, 13.2%, and 2.9% patients, respectively. Most of the patients with BPN had mild hyponatremia (89%). The prevalence of hyponatremia was significantly higher in children aged 6-10 years [odds ratio (OD)=4.29, 95% confidence interval (CI)=0.90-20.45, p<0.05], females (OR=0.56, 95% CI=0.32-0.96, p=0.03) and cases of empyema (OR=4.49, 95% CI=1.48-13.60, p=0.008).

Conclusion: In conclusion, among children hospitalized with LRTI, an older age (6-10 years), being female, and the presence of empyema are significant risk factors for the development of hyponatremia. In such children, serum electrolytes should be regularly measured to prevent adverse clinical outcomes.

Keywords: Bronchopneumonia, electrolyte, hyponatremia, lower respiratory tract infection

Introduction

Lower respiratory tract infection (LRTI) is an inflammation of the airways (pulmonary tissue), due to viral or bacterial infection, below the level of the larynx. LRTI includes various diseases such as: bronchiolitis, wheeze-associated LRTI (WALRI), bronchopneumonia (BPN), Lobar pneumonia and Empyema. LRTI is one of the serious illnesses requiring hospitalization especially in children under 5 years of age. It accounts for 30% of deaths annually worldwide mostly due to pneumonia as the leading cause (1).

In the last 10 years, changes have been observed in the epidemiology of LRTIs as there has been a reduction in the burden in children below 5 years of age and an increased burden has been observed in patients over 70 years of age.

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Received: *25.02.2021* **Accepted:** *16.05.2021*

Among all ages, pneumococcal pneumonia was responsible for 55.4% of LRTI deaths (2).

Patients with pneumonia and bronchiolitis, the most common diseases encountered in paediatric general practice, are at particular risk of developing hyponatremia due to anti-diuretic hormone (ADH) over-secretion (3-5).

Several ongoing studies are being conducted to determine any correlation between hyponatremia and acute LRTI in children as there is growing interest in the issue of sodium imbalance in different types of LRTI (1). Singh et al. (6) conducted a study on hyponatremia in different types of LRTI and found hyponatremia in 33% cases out of a total 100 cases (51.5% mild, 42.5% moderate and 6% severe). A similar study conducted by Chaitra et al. (1) found hyponatremia in 45% out of 91 cases (70.7% mild, 21.9% moderate and 7.3% severe). However, there are few studies on Indian children and the western data may not aptly apply to the Indian subpopulation.

This study was carried out to characterize the association between hyponatremia in those patients admitted to a paediatric ward, in the setting of acute LRTI in different age groups and to determine the association between the severity of hyponatremia and different types of acute LRTI in children.

Methodology

A prospective observational study was conducted on the paediatric age group (1 month to 12 years) presenting with symptoms and signs suggestive of acute LRTI from December 2017 to June 2019. This study was approved by the Institutional Ethical Committee. After the child had met the inclusion criteria, informed consent was obtained from the guardian or the parent after explaining the aims of the study to him or her.

Exclusion criteria:

- Known case of congenital heart disease
- Known case of renal disease
- History of recent surgery
- Any child with a previous diagnosis of syndrome of inappropriate antidiuretic hormone
- Known case of bronchial asthma
- Febrile seizures
- Patient with acute gastroenteritis
- Cystic fibrosis
- Pan-hypopituitarism
- Hypothyroidism
- Metabolic diseases
- Chromosomal or genetic disorders
- Meningitis

The sample size calculation was based on the prevalence of hyponatremia as seen in the study of Chaitra et al. (1) among LRTI children. A sample size of 170 children was calculated by means of Fisher's formula.

Complete history, physical examination, relevant laboratory investigation, and radiological investigations were examined to confirm the diagnosis. Pneumonia was diagnosed in patients presenting with fever, tachypnoea, dyspnoea, grunting, and chest retraction. BPN and lobar pneumonia were further differentiated on the basis of chest X-ray (patchy opacity in BPN and lobar involvement in lobar pneumonia). WALRI was diagnosed as signs and symptoms of respiratory obstruction and wheeze without any family history or atopy. Wheezing refers to a high-pitched whistling sound audible without auscultation. Bronchiolitis was confirmed on the basis of tachypnoea, rhinorrhoea, crepitation, wheeze, subcostal and intercostal retraction, nasal flaring, grunting and chest X-ray showing hyperinflation. Empyema was characterized by systemic toxicity, breathing difficulty, decreased movement of the chest, decreased air entry, dull percussion note, and obliteration of the costophrenic angle with varying degrees of opacification in chest X-ray.

After obtaining consent from the parent, 2 mL of blood was taken from each patient using the aseptic technique and this sample was put in a vacutainer. The blood samples were then transported to the emergency laboratory within an hour of collection for analysis and reports were collected. Analysis was carried out to determine for which particular group of respiratory illness was the association of hyponatremia more significant. The patients were divided into age groups as 1 month to 12 months, 1-3 years (12 months to 36 months), 3-6 years, 6-10 years, and 10-12 years. Serum sodium level was measured in our hospital based on the principle of indirect ion selective electrode with the Beckman Coulter AU480 fully automated biochemistry analyser.

The prevalence of hyponatremia and the type of LRTI was noted in the children. Hyponatremia was graded into mild, moderate and severe grades.

Statistical Analysis

The results are presented as frequencies, percentages and mean ± standard deviation. The chi-square test was used to assess the associations. The unpaired t-test was used

to compare continuous variables. Binary logistic regression analysis was carried out to determine the strength of association. The odds ratio (OR) with its 95% confidence interval (CI) was calculated. A p-value <0.05 was considered significant. All the analysis was carried out on SPSS 16.0 version (Chicago, Inc. USA).

Results

The mean age of the study patients was 1.88±2.41 years with 146 (63.2%) males and 85 (36.8%) females.

Out of all the cases of LRTI, there was the highest number of cases for BPN (61%), followed by empyema (12.6%), lobar pneumonia (9.5%), bronchiolitis (9.1%) and the lowest number of cases of WALRI (7.8%) (Figure 1).

The prevalence of hyponatremia was found to be 58.9% (Out of 231 cases, hyponatremia was present in 136 cases and absent in 95 cases). Mild hyponatremia was the most common (83.8%) followed by moderate (13.2%) and then by severe hyponatremia (2.9%).

About half of the patients were 1-12 months (51.5%) followed by 1-3 years (35.1%), 3-6 (6.9%), 6-10 years (5.2%) and lastly 10-12 years (1.3%).

The prevalence of hyponatremia was highest in the age group 10-12 years (100%) and lowest in the age group 1-12 months (53.8%). However, as the number of cases was only three in the age group 10-12 years, we cannot make any conclusion on this basis. Prevalences in the 6-10 years group, the 1-3 years group and the 3-6 years group were 83.3%, 61.7% and 56.2% respectively. The prevalence of hyponatremia was 4.29 times higher in the 6-10 years group than the 1-12 months group (OR=4.29, 95% CI=0.90-20.45, p<0.05) (Table I).

The prevalence of hyponatremia was higher in females (66.7%) than males (53%) with a significantly higher risk (OR=0.56, 95% CI=0.32-0.96, p=0.03) (Table II).

The prevalence of hyponatremia was highest in empyema (86.2%) and was lowest in WALRI (22.2%). The risk association showed a significantly increased risk of hyponatremia in empyema (OR=4.49, 95% CI=1.48-13.60, p=0.008) and decreased risk in WALRI (OR=0.20, 95% CI=0.06-0.65, p=0.008) (Table III).

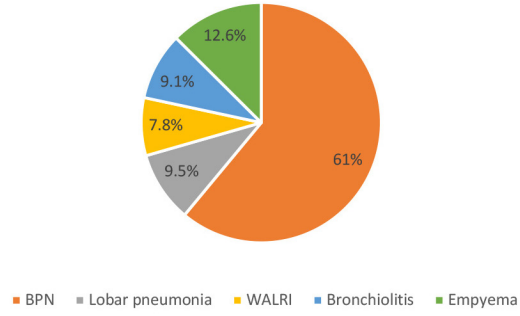

Figure 1. Shows the overall distribution of LRTI
BPN: Bronchopneumonia, LRTI: Lower respiratory tract infection, WALRI: Wheeze-associated LRTI

Table I. Comparison of prevalence of hyponatremia with age in LRTI

Age in months	No. of patients		Hyponatremia				OR (95% CI)	p-value
		Present		Absent				
	No.	%	No.	%	No.	%		
1-12 months	119	51.5	64	53.8	55	46.2	1.00 (Ref.)	
1-3 years	81	35.1	50	61.7	31	38.3	1.38 (0.78-2.46)	0.26
3-6 years	16	6.9	9	56.2	7	43.8	1.10 (0.38-3.16)	0.85
6-10 years	12	5.2	10	83.3	2	16.7	4.29 (0.90-20.45)	0.06
10-12 years	3	1.3	3	100.0	0	0.0	-	-

OR: Odds ratio, CI: Confidence interval, No.: Number, LRTI: Lower respiratory tract infection

Table II. Comparison of prevalence of hyponatremia with gender in LRTI

Gender	No. of patients		Hyponatremia				OR (95%CI)	p-value
		Present		Absent				
	No.	%	No.	%	No.	%		
Male	132	57.1	70	53.0	62	47.0	0.56 (0.32-0.96)	0.03*
Female	99	42.9	66	66.7	33	33.3	1.00 (Ref.)	

OR: Odds ratio, CI: Confidence interval, No.: Number, LRTI: Lower respiratory tract infection

Based on the type of LRTI (Table III):

1) BPN had 89% mild hyponatremia, 9.8% moderate hyponatremia and 1.2% severe hyponatremia.

2) Lobar pneumonia had 85.7% mild hyponatremia, 14.3% moderate hyponatremia and 0% severe hyponatremia.

3) WALRI had 100% mild hyponatremia.

4) Bronchiolitis had 72.7% mild hyponatremia, 27.3% moderate hyponatremia and 0% severe hyponatremia.

5) Empyema had 68% mild hyponatremia, 20% moderate hyponatremia and 12% severe hyponatremia.

Discussion

Hyponatremia is a significant electrolyte abnormality commonly seen in hospital-admitted children with LRTI. The underlying mechanism is the release of excess ADH (7-10). The current study has importance as it illustrates an association of hyponatremia with different types of LRTI among children (11,12).

Literature reports hyponatremia to be in the range of 6% to 73%. Our results fell within the reported range as we found hyponatremia in 136 (58.9%) cases.

Out of all the cases of hyponatremia, 83.8% cases had mild hyponatremia, and 13.2% and 2.9% cases had moderate and severe hyponatremia, respectively. Our findings corroborated the previous studies which reported the majority of cases with mild hyponatremia (13-18). Among these studies, the prevalence of mild cases of hyponatremia was significantly more in developed countries when compared to developing countries; thus highlighting the improved care and management in developed countries.

Our study results showed that the age group of 6-10 years carried a significantly increased risk of hyponatremia in relation to other age groups (OR=4.29, 95% CI=0.90-20.45, p>0.05). This may be because the inherent capacity of the body to balance the electrolytes decreases with advancing age in children. Secondly, it could be because children of less than 5 years of age are managed more effectively and care is given to prevent the occurrence of hyponatremia. Among the previous studies, the association of hyponatremia has been studied mainly in the age group of 2-month-old to 5-year-old children (18) and thus very few studies have reported on the age association of hyponatremia. Wrotek and Jackowska (19) found that the age group of >4 years has a greater chance of hyponatremia and severe infection. Park et al. (13) found that increasing age is an independent risk factor for the development of hyponatremia (OR=1.007, 95% CI 1.002-1.012, p=0.006). Our study has strength in validating this relationship of hyponatremia with age as this may warn clinicians who manage children.

Another interesting association seen in the present study was that females carried a significantly increased risk of hyponatremia when compared to males. Relatively few studies have reported on the demographic association of children with hyponatremia and some with contrasting results to the present study. Park et al. (13) found that males are more prone to hyponatremia (OR=1.361, 95% CI 1.105-1.675, p=0.004) and Sakellaropoulou et al. (20) found no significant difference in the gender distribution of children having hyponatremia. The higher risk of hyponatremia in females in the present study may be due to their late presentation in the hospital since ours is a male dominant society where medical care for female children may not be availed at an early stage.

In our endeavour to determine the relationship of hyponatremia with different etiologies of LRTI, it was observed that hyponatremia carried a significantly higher risk in empyema (OR=4.49, 95% CI=1.48-13.60, p=0.008) and lower risk in WALRI (OR=0.20, 95% CI=0.06-0.65, p=0.008). This may be ascribed to the seriousness of the disease. On one hand, empyema is a bacterial disease serious enough to require invasive treatment modalities

Table III. Comparison of prevalence of hyponatremia with type of LRTI

Type of LRTI	No. of patients		Hyponatremia				OR (95%CI)	p-value
		Present		Absent				
	No.	%	No.	%	No.	%		
BPN	141	61.0	82	58.2	59	41.8	1.00 (Ref.)	
Lobar pneumonia	22	9.5	14	63.6	8	36.4	1.25 (0.49-3.19)	0.62
WALRI	18	7.8	4	22.2	14	77.8	0.20 (0.06-0.65)	0.008*
Bronchiolitis	21	9.1	11	52.4	10	47.6	0.79 (0.31-1.98)	0.61
Empyema	29	12.6	25	86.2	4	13.8	4.49 (1.48-13.60)	0.008*

OR: Odds ratio, CI: Confidence interval, BPN: Bronchopneumonia, LRTI: Lower respiratory tract infection, WALRI: Wheeze-associated LRTI, No.: Number

of pus drainage and culture sensitivity; and on the other hand, WALRI is a viral infection causing wheezing in the chest which can be managed well. This also corroborated with the findings wherein mild cases of hyponatremia were observed in all children with WALRI, whereas in empyema, 32% had moderate to severe hyponatremia. Other clinical conditions such as BPN, lobar pneumonia and bronchiolitis were intermediate in the risk for hyponatremia without any statistical significance ($p>0.05$). In the study by Park et al. (13), children with acute tonsillopharyngitis had the highest incidence of hyponatremia (44.1%). Kaneko (21) found that hyponatremia was more common when the deeper inflammatory sites of the respiratory tract were involved such as in cases of pharyngitis (13.3%), bronchitis or bronchiolitis (22.9%), and pneumonia (38.7%).

One factor causing increased hyponatremia in empyema in our study could be because such children have high TLC counts and inflammation. Although the present study did not assess WBC counts or CRP levels, Park et al. (13) found a significantly higher WBC counts and CRP levels in acute tonsillopharyngitis, indicating that increasing inflammation may be associated with the severity of hyponatremia.

The underlying mechanism remains an enigma although current concepts favour the involvement of syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in the causation of hyponatremia. It has been proposed that fever resets the hypothalamic thermostat and osmostat (for ADH secretion) in children. The new osmostat increases the secretion of ADH, causing fluid retention and decreased osmolarity in the body, thereby leading to hyponatremia (8,10).

Based on the current study results and the study by Park et al. (13), it can be postulated that SIADH may be the result of inflammation wherein the cytokines surge of interleukin (IL)-1β and IL-6 form the primary mediators causing increased ADH secretion and SIADH. This has been indirectly evidenced in a study on rats which showed that IL-1β stimulated both the peripheral and central release of vasopressin (22). Further, the stimulated release of arginine vasopressin (AVP) by IL-6 was seen in the study by Palin et al. (23) through "magnocellular AVP-secreting neurons". Previously, two studies on pneumonia observed an inverse relationship between inflammatory markers and serum sodium levels (19,24). In our cohort, we also found that hyponatremia was significantly increased in cases of empyema among various LRTI, and the risk association was significant with an OR of 4.49.

Literature is sparse regarding studies which evaluated the factors affecting the fall in sodium levels in children with respiratory tract infections (13). Our study has strength in showing an age and gender association with hyponatremia in children with LRTI. Additionally, we also determined the etiological risk associated with hyponatremia. However, we failed to determine the role of co-infection in hyponatremia.

Study Limitations

Our study was also limited by its cross-sectional design wherein we could not suggest the association of hyponatremia with hospitalisation and mortality. Another limitation of the study was that it was conducted in general paediatric ward, and not in an ICU. This might have created a potential bias in the prevalence of hyponatremia among different children with LRTI. Lastly, since our study centre was a referral centre, many sick babies were referred to the hospital from various hospitals and their treatment status was not known.

Conclusion

In conclusion, among those children hospitalized with LRTI, an older age (6-10 years), being female, and the presence of empyema are significant risk factors for the development of hyponatremia. In such children, serum electrolytes should be regularly measured to prevent adverse clinical outcomes.

Ethics

Ethics Committee Approval: The study was approved from the Institutional Review Board Ethical Committee (IEC/ROHTAK/2018/16-4).

Informed Consent: Informed consent was obtained from the guardian or the parent after explaining the aims of the study to him or her.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Design: S.S., R.K., R.K.J., Data Collection or Processing: S.S., R.K., R.K.J., T.K.L., Analysis or Interpretation: C.M., R.K.J., Literature Search: S.S., C.M., R.K., R.K.J., Writing: R.B.G.B., R.D.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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J Pediatr Res 2021;8(4):485-90
DOI: 10.4274/jpr.galenos.2021.08634

Original Article

Diagnosis, Treatment and Follow-up of Fetal Cardiac Arrhythmia

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ABSTRACT

Aim: The importance of managing fetal arrhythmia has increased with advances in fetal echocardiography. We aimed to describe the incidence, types, clinical characteristics, treatments, and follow-ups of patients diagnosed with fetal arrhythmia in our center.

Materials and Methods: Fetal echocardiographic examinations performed in our units between January 2016 and September 2019 were retrospectively evaluated. Fetal arrhythmias and their subtypes were identified using M-mode and Doppler echocardiography in all patients. Maternal age, gestational age, history of maternal or gestational pathology, diagnoses, and medications were recorded. Fetal arrhythmias were categorized into three main groups: 1) Irregular heart rhythm (ectopic beats), 2) Bradyarrhythmias: a ventricular rate less than 110 bpm; and 3) Tachyarrhythmias: a ventricular rate exceeding 180 bpm.

Results: A total of 60 patients were diagnosed with fetal arrhythmia, corresponding to an overall incidence of 0.5%. The mean maternal and gestational age of those patients with fetal arrhythmia were 28.35±4.88 years and 31.03±5.94 weeks. One patient had maternal systemic disease, and four had concurrent congenital cardiac disease. Fetal tachycardia, bradycardia, and irregular heart rhythm were detected in 10 (16.6%), 8 (13.3%), and 42 (70%) patients, respectively.

Conclusion: Fetal echocardiography represents the main diagnostic tool for prenatal evaluation of fetal arrhythmias, which have a variable prognosis depending on the type of arrhythmia. The most common fetal arrhythmia, the irregular heart rhythm, generally does not necessitate any treatment and resolves spontaneously. The treatment plan in patients should be based on etiology and fetal conditions.

Keywords: Fetal echocardiography, fetal arrhythmia, tachycardia, bradycardia, irregular heart rhythm

Introduction

The development of fetal echocardiography has led to an increased awareness among clinicians regarding the importance of fetal arrhythmia management (1). Although most fetal arrhythmias are of benign nature, certain types of arrhythmias may be associated with certain adverse consequences such as fetal hydrops, cardiac dysfunction, and even fetal mortality (2). Therefore, fetal heart rate (FHR) should be evaluated carefully in all pregnancies.

The detection of normal fetal cardiac rhythm is based on the documentation of regular atrial and ventricular rhythm, with a normal rate for gestational age. Each atrial activity is followed by a ventricular activity within the framework of a normal atrio-ventricular (AV) time interval, corresponding to a normal AV conduction rate of 1:1 (3).

Currently, echocardiography represents the most widely used tool for diagnosis and follow-up of fetal arrhythmias in clinical practice. Although non-invasive techniques to record electrophysiological signals from the fetal heart have been

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Received: *04.03.2021* **Accepted:** *07.05.2021*

developed and have proven valuable in gathering important information on the pathophysiology of arrhythmias, they are mainly used as research tools and only in a limited number of centers (4).

Perinatal management of fetal arrhythmia is important to improve the outcome of an affected fetus. Accurate prenatal diagnosis is crucial for the selection of appropriate prenatal and postnatal treatments. In this study, we aimed to describe the incidence, types, clinical characteristics, treatments, and follow-ups of those patients diagnosed with fetal arrhythmia in our center.

Materials and Methods

Fetal echocardiographic examinations performed in our secondary and tertiary healthcare units between January 2016 and September 2019 were retrospectively evaluated. Fetal arrhythmias and their subtypes were diagnosed with M-mode and Doppler echocardiography in all patients. Maternal age, gestational age, history of maternal or gestational pathology, diagnoses, and medications were recorded in those patients diagnosed with fetal arrhythmia. This study was approved by the University of Health Sciences Turkey, Tepecik Training and Research Hospital Clinical Researches Ethical Committee (no: 2020/11-66).

Initially, signs of structural cardiac abnormality or cardiac failure were investigated in all fetuses. In those diagnosed with fetal arrhythmia, the type of arrhythmia was ascertained using M-mode echocardiography and Doppler ultrasound. Simultaneous atrial and ventricular wall movements were examined via M-mode echocardiography, while the type of arrhythmia was determined using the mitral inflow and aortic outflow (mitral valve flow/aorta flow) technique via Doppler echocardiography.

Classification of Fetal Arrhythmias

Fetal arrhythmias were assessed in three main groups: 1) Irregular heart rhythm (ectopic beats); supraventricular premature beats and ventricular premature beats; 2) Bradyarrhythmias: ventricular rate less than 110 bpm (sinus bradycardia, 2:1 AV block, complete AV block), and 3) Tachyarrhythmias: Ventricular rate exceeding 180 bpm [sinus tachycardia, supraventricular tachycardia (SVT), ventricular tachycardia (VT)].

Statistical Analysis

We used the Statistical Package for Social Sciences (SPSS, version 23.0, SPSS Inc., Chicago, IL, USA). Descriptive analysis was used for demographic, clinical, and medication variables.

Results

Between January 2016 and September 2019, a total of 12,002 patients underwent fetal echocardiography. Among these, 60 were diagnosed with fetal arrhythmia. Clinical presentation included irregular rhythm in 42 patients, bradycardia in 8, and tachyarrhythmia in 10. These findings corresponded to a fetal arrhythmia incidence of 0.5% in the overall study population.

The mean maternal age in those patients with fetal arrhythmia was 28.35±4.88 years (minimum: 19, maximum: 38 years), while the gestational age was 31.03±5.94 weeks. One patient had maternal systemic disease, and 4 had concomitant congenital cardiac disorders. The demographic and clinical characteristics of patients with fetal arrhythmia are shown in Table I.

Ten patients, with an average maternal age of 29.2±3.64 years and gestational age of 31.4±6.36 weeks, had fetal tachycardia. All cases with fetal tachycardia had SVT. One patient with SVT had a cardiac anomaly consisting of a single ventricle defect and died in the first postnatal week after birth at 33 weeks of gestation.

Bradycardia was present in 8 patients, who had an average maternal age of 26.00±4.40 years and gestational age of 27.7±5.47 weeks. Dexamethasone treatment was started in one patient diagnosed at 29 weeks of gestation who had maternal antibody positivity. This patient was born at 38 weeks of gestation, with a heart rate between

Table I. Demographic and clinical characteristics in patients with fetal arrhythmia

	n=60
Gestational age (weeks) (mean ± SD)	31.03±5.94
Maternal ages (years) (mean ± SD)	28.35±4.88
Congenital heart disease n (%)	4 (6.6)
Maternal disease n (%)	1 (1.6)
Mortality n (%)	3 (5)
Fetal tachycardia n (%)	10 (16)
Maternal ages (years)	29.2±3.64
Gestational age (weeks)	31.4±6.36
Fetal bradycardia n (%)	8 (13.3)
Maternal ages (years)	26.00±4.40
Gestational age (weeks)	27.7±5.47
Irregular cardiac rhythm n (%)	42 (70)
Maternal ages (years)	28.28±5.23
Gestational age (weeks)	32.09±5.15

SD: Standard deviation

80 and 90 bpm. Another patient with left atrial isomerism and AV septal defect (AVSD) was diagnosed at 23 weeks of gestation. Although salbutamol was started, this was followed by a subsequent termination of the pregnancy. A further patient with AV block had a heart rate between 60 and 70 bpm, and was only followed up due to the absence of signs of hydrops. 4 other patients had sinus bradycardia, with a heart rate greater than 60 bpm, and these patients did not receive any medical treatment due to an absence of the signs of heart failure or hydrops. Additionally, no signs of cardiac failure were observed during their follow-up period.

Forty-two patients were found to have irregular heart rhythm. The mean maternal and gestational ages in these patients were 28.28±5.23 years and 32.09±5.15 weeks, respectively. Among these, only one patient had diaphragmatic herniation and supraventricular premature beats coexisting with dextrocardia. In the remaining cases, no cardiac pathology was found. The patient with diaphragmatic herniation died at postnatal 24 hours. The irregular heart rhythms were normalized in the remaining group.

Thus, the majority of our patients diagnosed with fetal arrhythmia had irregular cardiac rhythm (70%), followed by SVT (16.6%), and bradycardia (13.3%). Their echocardiographic results, clinical findings, and outcomes of arrhythmia are shown in Table II.

Discussion

Fetal arrhythmias occur in a small percentage (0.6-2.0%) of all pregnancies (5,6), and the frequency of pediatric cardiologic referral of these patients is reported to be between 10% and 20% (7). Incidence rates have not been provided in some previous studies due to the admission of patients specifically diagnosed with fetal arrhythmia to tertiary referral centers (8). However, we chose to present such data since patients from a secondary healthcare facility were also included in the sample population, in addition to a tertiary center. Thus, based on our results, the incidence of fetal arrhythmia was in the order of 0.5%.

Fetal Tachycardia

Tachycardia is generally defined as the presence of sustained FHR exceeding 180 bpm. The detection of a fast heart rate greater than 180 bpm in a fetus constitutes a medical emergency since it may lead to fetal hydrops or premature delivery as well as increased perinatal morbidity and mortality. Sustained tachycardia with high ventricular rate in the early gestational weeks is more likely to be associated hydrops with fetalis. In the current study, two patients had signs of hydrops fetalis due to SVT occurring at 22 and 25 weeks of gestation.

The causes of fetal tachycardia include sinus tachycardia, re-entrant SVT, atrial flutter, atrial ectopic tachycardia, junctional ectopic tachycardia, and VT. Among these, re-entrant SVT represents the most common type of fetal tachycardia (9), comprising almost two-thirds of all cases with this condition (5). Re-entrant tachycardia mostly occurs between 24 and 32 weeks of gestation. Eight of our patients with a mean gestational age of 31.4±6.36 weeks had re-entrant tachycardia. The second most common type of tachycardia was AF, which was detected in two cases. Conversely, junctional ectopic tachycardia and VT are uncommon and were not identified in any of our patients. Approximately 2% of those patients with fetal tachycardia have been reported to have coexisting congenital cardiac disorders (10,11). In another study, 15% to 18% of fetuses with fetal arrhythmia were also found to have concomitant congenital cardiac abnormalities (12). In our study, congenital cardiac disorder was present in 12.5% of those patients with SVT and in 6.6% of those with fetal arrhythmia.

In one study involving 29 cases diagnosed with fetal arrhythmia, the subtypes were fetal tachycardia, fetal bradycardia, and irregular heart rhythm in 41.4%, 17.2%, and 41.4% of the cases respectively (13). In the current study 16.6% of those patients with fetal arrhythmia had fetal tachycardia, and the most common type was irregular heart rhythm.

Currently, there is no consensus regarding the first agent of choice for the treatment of re-entrant SVT, and the decision should be based on the condition of the fetus. For a non-hydropic fetus, the commonly used drugs are sotalol, flecainide, and digoxin, while flecainide and sotalol have been shown to be readily transferred through the placenta and therefore may be used for hydropic fetuses (14). In a study by Jaeggi et al. (15), flecainide was found to be slightly more effective than sotalol in hydropic fetuses. When no response is obtained with single-agent therapy, combinations may be tried, such as amiodarone/digoxin, amiodarone/flecainide, sotalol/digoxin, and sotalol/flecainide on the basis of studies reporting their benefits (15,16). Arrhythmia was terminated with digoxin in all of our patients with re-entrant SVT.

Currently, digoxin and sotalol are used to treat AF, with sotalol preferred in the presence of hydrops. Of our two cases with AF, one responded to digoxin, while the other was followed up with digoxin/sotalol combination therapy.

Table II. Echocardiographic results, clinical findings, and outcome of arrhythmia by subtype

Fetal arryhtmia type	Incidence	Echocardiographic findings	Clinical findings	Treatment	Outcome
Tachycardia	**0.08%**				
Case 1 (week 25)		Hydrops fetalis	Atrial flutter	Digoxin Sotalol	Birth: 36th week recurrent episodes of SVT in postnatal period Cured with propranolol
Case 2 (week 22)		Hydrops fetalis	Re- entrant SVT	Digoxin Sotalol	Birth: 34 week SVT disappeared in postnatal period
Case 3		Single ventricle defect	Atrial flutter	Digoxin	Recurrent episodes of SVT and patients died
Case (4,5,6,7,8,9,10)		Normal	Re- entrant SVT	Digoxin	SVT disappeared
Bradycardia	**0.06%**				
Case 1		Left atrial isomerism - AVSD	cAV block bradycardia	Salbutamol	Patient died in fetal period
Case 2		Normal	cAV block bradycardia	-	Followed in postnatal period
Case 3		Maternal Anti-Ro + Normal	cAV block bradycardia	Dexamethasone	Cured with dexamethasone
Case 4		Aortic arch hypoplasia	Bradycardia	-	Bradycardia disappeared in postnatal period
Case (5,6,7,8)		Normal	Sinus bradycardia	-	Postnatal normal
Irregular heart rhythm	**0.34%**			**-**	
Case 1		Dextrocardia, diafragmatic hernia	Ectopic beats	-	Patient died in postnatal period
Case 2-42		Normal	Ectopic beats	-	Normal

SVT: Supraventricular tachycardia, cAV: Complete atrioventricular, AVSD: Atrio-ventricular septal defect

However, this latter patient died at postnatal week 1 due to a coexisting cardiac anomaly.

Fetal Bradyarrhythmia

Fetal bradycardia is defined as a regular heart rate below 100-110 bpm without taking the gestational age of the fetus into consideration (6). It may be caused by sinus bradycardia, premature atrial contractions (PAC) with block, or AV block. Transient bradycardia, generally occurring during the second trimester, is benign and does not require treatment (14).

Persistent fetal bradycardia is relatively rare. Slow heart rate may develop due to a congenital or acquired injury in the sinoatrial node. Possible causes include viral myocarditis, inflammation and fibrosis due to collagen tissue disorders, maternal treatment with β blockers and sedatives, fetal distress, hypoxia or acidosis. Additionally, in patients with persistent sinus bradycardia, long-QT syndrome should be investigated during the postnatal period. According to Mitchell et al. (17), 40% of long QT syndrome cases evaluated by fetal magnetocardiography were referred due to sinus bradycardia.

Nearly 50% of cases with complete AV block are associated with complex cardiac malformations (18) (left atrial isomerism, AV septal defect, corrected transposition of the great arteries) or maternal autoantibodies (associated with autoimmune diseases such as systemic lupus erythematosus) (19).

Of the three patients with complete AV block in our study, two had coexisting anomalies (one had left atrial isomerism and AVSD, and one had maternal anti-Ro antibody positivity). In this regard, it should be remembered that the combination of complete AV block and major structural heart disease carries high mortality. When hydrops is present, the mortality rate approaches 100% (5). In this study, the pregnancy associated with fetal left atrial isomerism was terminated.

Treatment of fetal bradycardia depends on the etiology, ventricular rate, and presence or absence of cardiac failure. If the FHR is less than 55 to 60 bpm, beta-mimetics (terbutaline, salbutamol, isoprenaline) may be tried as a first line therapy (14,20). These agents may increase the

fetal ventricular rate by around 10-20% and reverse hydrops as well (21). Immune-mediated AV block may benefit from in utero treatment with fluorinated steroids, intravenous immunoglobulin, or both. Dexamethasone is believed to reduce inflammation (22). Although no consensus exists, many clinicians administer dexamethasone 4 to 8 mg/d to treat second degree AV block, recent onset AV block, or severe cardiac dysfunction and hydrops. In our study, salbutamol treatment was given during the fetal period in the patient with atrial isomerism-AVSD, while the other patient with maternal antibody positivity benefited from dexamethasone.

Irregular Cardiac Rhythm

Irregular heart rhythm, also called premature beat, premature contraction, ectopic beat or extra-systole, can originate from the atria, the AV junction, or the ventricle, and bypasses the sinus node. Irregular heart rhythms are the most common abnormal rhythms seen in clinical practice.

Fetal ectopy occurs in up to 1 to 2% of all pregnancies and has been reported to be a relatively benign condition (5). In a study by Capuruço et al. (23), fetal ectopic beats were the most common type of fetal arrhythmia with an incidence of 55.5%. Similarly, this was also the most common fetal arrhythmia, occurring in 70% of our patients. In our study, 0.34% of all pregnancies were associated with irregular heart rhythm. Most irregular beats originate from the atrium (PAC), with premature ventricular contractions (PVC) being much less frequent than PAC, with an estimated prevalence ratio of 10:1 for PAC vs. PVC (24). In clinical practice, ectopic beats are mostly detected in the third trimester of pregnancy (7). Similarly, in this study, the mean gestational age of patients with irregular heart rhythm was 32.09 weeks.

The majority of fetuses evaluated for irregular rhythm have a structurally normal heart. In a recent study of 256 singleton fetuses with an irregular heart rhythm, only two (0.8%) had a congenital heart malformation (25). In our study, only one patient among 42 cases (2.3%) had a coexisting cardiac anomaly. In another report describing 306 fetuses with irregular rhythm, isolated extrasystoles were diagnosed in 298 and were still present in 10 (3.4%) at delivery (26). Among our patient group, 1 (2.3%) had extra-systoles that persisted for up to 3 days following delivery. In patients with fetal ectopic beats, the risk of developing fetal tachycardia is estimated to be between 0.5% and 1%. The presence of couplets and blocked atrial bigeminy increases this risk to approximately 10%. Fetal ectopic beats are generally of benign nature, most resolving spontaneously. No medical treatment is considered necessary for these patients although it is recommended that these patients should be assessed on a weekly basis with respect to SVT and VT (14).

Study Limitations

The absence of long-term follow-up findings in the postnatal period can be assessed as a limitation of our study.

Conclusion

Fetal echocardiography represents the main diagnostic tool for prenatal evaluation of fetal arrhythmias. In all patients with suspected tachyarrhythmia or bradyarrhythmia, a fetal echocardiography should be performed to evaluate cardiac structures and functions. Fetal arrhythmias may present with variable types and prognostic consequences, with no direct effects on fetal growth and development. The etiology and fetal conditions are the main determinants of the management strategy for fetal tachyarrhythmias and bradyarrhythmias.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, Tepecik Training and Research Hospital Clinical Researches Ethical Committee (no: 2020/11-66).

Informed Consent: Informed consent was not obtained because this was a retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: A.Ş., T.D., Data Collection or Processing: T.D., Analysis or Interpretation: A.Ş., T.D., Literature Search: A.Ş., T.D., Writing: A.Ş.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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J Pediatr Res 2021;8(4):491-7
DOI: 10.4274/jpr.galenos.2021.72623

Original Article

The Effects of Smartphone, Tablet and Computer Overuse on Children's Eyes During the COVID-19 Pandemic

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ABSTRACT

Aim: Due to restrictions during the Coronavirus disease-2019 (COVID-19) pandemic, smartphone, tablet and computer (STC) overuse might occur. There were some concerns that light sources which emit blue light might affect anterior and posterior segment structures. We investigated the effects of STC overuse on children's eyes during the pandemic.

Materials and Methods: Sixty-four children's findings at baseline (the early period of the pandemic) (group 1) were compared with those after 1 year (group 2). Correlations between daily STC use time (DSTCUT) and the ocular parameters in group 2 were evaluated.

Results: Compared to group 1, group 2 had longer DSTCUT (1.49±0.33 vs 5.62±0.57 hours, p<0.001), lower tear break-up time (TBUT) (12.70±1.45 vs 9.50±2.10 seconds, p=0.015), higher ocular surface disease index (OSDI) score (14.52±4.19 vs 25.22±5.75, p=0.007), more myopic spherical equivalent refraction (SER) (-1.00±0.30 vs -1.80±0.40 dioptres, p=0.031), and greater axial length (22.69±0.43 vs 23.42±0.37 millimetres, p=0.038). Schirmer tests, central corneal thicknesses (CCT), keratometries, anterior chamber depths (ACD), lens thicknesses (LT), retinal nerve fibre layer thicknesses, choroidal thicknesses and macular thicknesses of groups were similar (p>0.05). In group 2 as DSTCUT increased, TBUT (r=-0.368, p=0.034) decreased, OSDI score (r=0.384, p=0.028) increased and more myopic SER (r=0.340, p=0.045) occurred.

Conclusion: To our knowledge, this is the first study in children to comprehensively investigate the effects of STC overuse during a pandemic on ocular surface, anterior and posterior segment structures together. We found that STC overuse during the pandemic might increase the tendency to dry-eye and myopia, and might cause axial elongation. We also determined that at 1-year follow-up, STC overuse had no effect on CCT, keratometry, ACD, LT, and posterior segment parameters.

Keywords: Smartphone, tablet, computer, children, eye, COVID-19 pandemic

Introduction

In children, the use of digital devices with a close-working distance, such as smartphones, tablets or computers (STC), has increased with their technological developments (1). These devices allow various activities, such as surfing the internet, playing games or drawing. Due to the restrictions during the Coronavirus disease-2019 (COVID-19) pandemic, the implementation of digital or e-learning approaches, instead of face-to-face education, has led to children being more likely to use STC. Moreover, as the time spent at home has increased during the pandemic, parents may give these devices to children more often to keep them busy. Therefore, as the duration of the pandemic extends, children might start to overuse these devices in daily life. The American Academy of Pediatrics recommends that daily screen use in children aged 5-18 years should not exceed 2 hours (2). The

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Received: *17.06.2021* **Accepted:** *06.07.2021*

COVID-19 pandemic can place a significant burden on health and the economy. Prolonged exposure to digital screens may cause serious health problems in children. Weight gain as a result of unhealthy nutrition habits and inadequate physical activity, a predisposition to the development of metabolic syndrome, musculoskeletal disorders, sleeping disorders, psychiatric problems and behavioural disorders may develop (3-5). In addition, there were some concerns that light sources which emit the blue light might affect the anterior and posterior segment structures of the eye (6-8). To our knowledge, this is the first study in children to comprehensively investigate the effects of STC overuse arising from the restrictions during the COVID-19 pandemic on the ocular surface, anterior and posterior segment structures together.

Materials and Methods

This study was performed with the approval of Tepecik Training and Research Hospital's Medical Research Ethical Committee (approval number: 2020/10-19) and in line with ethical principles of the Declaration of Helsinki. Detailed information about the study was given to the children and their parents, and the risks were explained. Written informed consent forms were received from the participants and their parents.

Seventy-two children aged 10-18 years, using STC for at least two years, and routinely maintaining a screen distance of approximate 20-60 cm were initially included in the study. The data of 64 cases attending the check-up examinations were evaluated. Children having ocular trauma or surgery, cases with a history of significant refractive errors in their parents, contact lens wearers, those having chronic ocular disease and/or systemic disease capable of affecting the ocular structures, and children with an initial spherical equivalent refraction (SER) outside the range of -1.75 dioptres (D) to +1.75 D were not included in the study.

The best-corrected visual acuity (BCVA) was obtained by means of a Snellen chart. Ocular structures were evaluated with a slit-lamp biomicroscope and 90 D lens. Intraocular pressure was measured by a Goldmann applanation tonometer. Cyclopentolate hydrochloride 1% (Sikloplejin R; Abdi İbrahim Company, Turkey) was applied three times with 10-minute intervals for cycloplegia. Axial length (AL), central corneal thickness (CCT), keratometry, anterior chamber depth (ACD), lens thickness (LT) and refraction were measured by the optical biometry (LenStar LS900, Haag-Streit Diagnostic, Switzerland) and autorefractor/keratometry (Topcon KR-1, Japan) devices. Retinal nerve fibre layer (RNFL) thicknesses of the central, superior-temporal, superior-nasal, nasal, inferior-nasal, inferior-temporal and temporal sections were automatically determined by means of an optical coherence tomography (OCT) device (Heidelberg Spectralis; Heidelberg Engineering, Germany). Choroidal thicknesses were measured from the central area, 500 µm nasal and 500 µm temporal quadrants by means of an OCT device in enhanced-depth imaging mode. The vertical distance between the first (Bruch's membrane) and the second (internal surface of the sclera) hyperreflective lines was used for choroidal thickness measurements (9). Macular thicknesses were automatically measured from 1 mm diameter central (foveal) area, 3 mm diameter inner (parafoveal) area and 6 mm diameter outer (perifoveal) area by means of an OCT device. The inner and outer macular areas were further divided into four quadrants (superior, temporal, inferior, nasal). Measurements of nine subareas were recorded. Only the right eyes of the children were included in the study. All measurements were made by the same "blinded" researcher between 09.00-11.00 a.m. The average value of the three measurements was recorded. The measured cycloplegic refraction was converted to SER by means of the formula "sphere power+½ cylinder power". Myopia was defined as SER<-0.50 D, hyperopia as SER> +0.50 D and emmetropia as -0.50≤ SER ≤+0.50 D.

Tear film break-up time (TBUT) and Schirmer test with anaesthesia were performed for dry-eye evaluation. In TBUT test, fluorescein strip (Fluorescein paper, Haag-Streit AG, Switzerland) was moistened with saline solution and touched to the lower fornix. Cases were told to keep their eyes open until the first dry spots were seen on the tear film under illumination with cobalt blue light. The time interval between the last blink and the formation of the first dry spots was measured. In Schirmer test with anaesthesia, proparacaine HCl 0.5% (Alcain; Alcon Company, Belgium) was administered, followed by a 5 minute wait. Schirmer test paper (SNO strips, Laboratory Chauvin, France) was placed on 1/3 outer edge of the lower eyelid. After 5 minutes, the amount of wetting on the paper was recorded (10). In research, the tear-film stability was mainly determined by means of TBUT test, while secretion and the amount of the tear film were measured by means of Schirmer test (11). In individuals, the presence, frequency and severity of dry-eye symptoms were determined by means of the ocular surface disease index (OSDI) questionnaire (10). In our study, unanswered questions due to unperformed activities in the OSDI questionnaire were not included in the scoring. The sum of valid answers was multiplied by 25, and the result was divided by the number of valid questions. Thus, the total OSDI score was determined. The children and their

parents were asked to keep a diary showing their STC use time and outdoor activity time for 2 weeks. Daily STC use time (DSTCUT) was calculated by dividing the total STC use time by 14. Daily outdoor activity time was calculated similarly. The clinical findings and ocular parameters at baseline (the early periods of the pandemic) (group 1) were compared with those after 1 year (group 2). Additionally, correlations between DSTCUT and ocular parameters were evaluated in group 2. All cases in group 2 had excessive DSTCUT for at least 6 months.

Statistical Analysis

Statistical analysis was made with the IBM-SPSS version 20 program. Continuous variables were expressed as mean ± standard deviation (minimum - maximum) values. The Kolmogorov-Smirnov test was used to examine whether the variables complied with normal distribution in groups. Comparisons of the groups were made by the paired sample t-test. Pearson correlation analysis was used to evaluate the effects of DSTCUT on ocular parameters. P<0.05 was regarded as statistically significant.

Results

The mean age of the children was 13.15±2.03 years initially. There were 34 (53.1%) males and 30 (46.9%) females. The BCVAs of all of the children were 20/20. The DSTCUT of group 2 was longer than that of group 1 (5.62±0.57 vs 1.49±0.33 hours, p<0.001). Compared to group 1, group 2 had significantly lower TBUT (12.70±1.45 vs 9.50±2.10 seconds, p=0.015), a higher OSDI score (14.52±4.19 vs 25.22±5.75, p=0.007), more myopic SER (-1.00±0.30 vs -1.80±0.40 D, p=0.031), and greater AL (22.69±0.43 vs 23.42±0.37 mm, p=0.038). Daily outdoor activity times, Schirmer test values, CCTs, keratometries, ACDs, LTs, RNFL thicknesses of all sections, central, nasal and temporal choroidal thicknesses, and macular thicknesses of all areas were similar in both groups (p>0.05). The clinical findings and ocular parameters of the groups are shown in Tables I and II.

In group 2, as DSTCUT increased, TBUT (r=-0.368, p=0.034) decreased, OSDI score (r=0.384, p=0.028) increased and more myopic SER (r=0.340, p=0.045) occurred. On the other hand, Schirmer test value, AL, CCT, keratometry value, ACD, LT, central RNFL thickness, central choroidal thickness and central macular thickness were not significantly correlated with DSTCUT in group 2 (p>0.05). The correlation results between DSTCUT and ocular parameters in group 2 are shown in Table III.

Discussion

As the duration of the pandemic extends, due to restrictions, children might make a habit of overusing STC compared to the early periods of the pandemic. In our study, group 2 had significantly longer DSTCUT compared to group 1. We thought that the distance education being applied more effectively over the course of time and the increasing use of STC for entertainment purposes at home might be responsible for this situation. Digital devices may affect the tear-film layer and ocular surface (12-14). In a cross-sectional study, Moon et al. (12) stated that children using a smartphone for approximate 3 hours daily had lower

Table I. The clinical findings and anterior segment parameters of the groups

Clinical findings and anterior segment parameters	Group 1 (Findings at baseline) Mean ± SD (range)	Group 2 (Findings after 1 year) Mean ± SD (range)	p[a]
Daily STC use time (hour)	1.49±0.33 (1-3)	5.62±0.57 (4-8)	<0.001*
Daily outdoor activity time (hour)	1.32±0.53 (0.5-3)	1.29±0.61 (0.5-3)	0.539
TBUT (second)	12.70±1.45 (10-15)	9.50±2.10 (7-14)	0.015*
Schirmer test (millimeter)	12.28±1.76 (10-15)	11.37±2.04 (9-15)	0.106
Total OSDI score	14.52±4.19 (9-22)	25.22±5.75 (18-40)	0.007*
SER (diopter)	-1.00±0.30 (-1.50/+0.25)	-1.80±0.40 (-2.50/-0.25)	0.031*
Axial length (millimeter)	22.69±0.43 (22.14-23.21)	23.42±0.37 (22.95-23.82)	0.038*
Central corneal thickness (micrometer)	541.74±17.28 (519-564)	542.23±15.74 (521-562)	0.893
Keratometry value (diopter)	42.65±1.35 (40.50-44.25)	42.70±1.45 (40.25-44.50)	0.704
Anterior chamber depth (millimeter)	3.65±0.17 (3.38-3.84)	3.64±0.19 (3.36-3.89)	0.735
Lens thickness (millimeter)	3.39±0.21 (3.11-3.68)	3.36±0.24 (3.07-3.74)	0.587

SD: Standard deviation, STC: Smartphone, tablet and computer, TBUT: Tear break-up time, OSDI: Ocular surface disease index, SER: Spherical equivalent refraction
[a]Paired sample t-test, *p<0.05 statistically significant

Table II. Posterior segment parameters of the groups

Posterior segment parameters	Group 1 (Findings at baseline) Mean ± SD (range)	Group 2 (Findings after 1 year) Mean ± SD (range)	p[a]
Retinal nerve fiber layer thickness			
Central (µm)	104.5±6.3 (91-115)	102.9±5.7 (86-112)	0.602
Superior-temporal (µm)	108.2±13.6 (92-128)	109.4±17.3 (85-132)	0.714
Superior-nasal (µm)	105.3±14.2 (86-125)	107.1±16.9 (88-129)	0.578
Nasal (µm)	83.7±11.6 (63-96)	82.8±9.4 (67-94)	0.805
Inferior-nasal (µm)	104.1±16.9 (81-124)	103.0±14.2 (83-120)	0.746
Inferior-temporal (µm)	102.8±10.4 (89-117)	104.7±15.3 (81-123)	0.527
Temporal (µm)	94.9±9.1 (79-112)	92.6±12.4 (76-114)	0.489
Choroidal thickness			
Central (µm)	301.6±23.4 (275-332)	290.8±27.2 (245-327)	0.071
Nasal (µm)	287.9±26.5 (253-319)	275.7±29.1 (223-308)	0.065
Temporal (µm)	294.8±29.2 (262-328)	286.3±25.7 (252-316)	0.084
Macular thickness			
Central area (µm)	276.2±46.7 (224-329)	274.5±42.9 (226-325)	0.419
Inner segment (µm)			
Superior	342.5±50.3 (287-395)	341.6±44.5 (291-389)	0.503
Temporal	334.6±59.7 (271-402)	336.8±52.9 (279- 397)	0.375
Inferior	341.2±48.3 (287-396)	340.1±45.6 (289-391)	0.487
Nasal	344.9±39.5 (298-389)	346.9±41.2 (297-394)	0.392
Outer segment (µm)			
Superior	293.5±56.8 (224-354)	293.0±52.3 (232-349)	0.624
Temporal	292.4±49.5 (235-346)	290.8±47.2 (237-342)	0.428
Inferior	284.7±42.8 (237-335)	286.8±45.7 (235-339)	0.380
Nasal	354.2±35.1 (309-392)	354.9±38.6 (308-397)	0.583

SD: Standard deviation
[a]Paired sample t-test, *p<0.05 statistically significant

TBUTs compared to those using it for less than 1 hour daily. They also showed that there was a significant increase in TBUT in children with dry-eye when smartphone usage was discontinued for 4 weeks (12). Wu et al. (14) found that computer workers with a daily digital screen time of more than 4 hours had significantly shorter TBUTs compared to those with the daily digital screen time of 4 hours or less. The authors detected that the Schirmer scores of both groups were similar (14). On the other hand, Nakamura et al. (15) stated that, in office workers, the duration of computer use did not affect TBUT measurement. They reported that office workers using a computer for more than 8 hours per day had significantly lower Schirmer scores compared to those using it for less than 2 hours per day (15). In our study, the TBUT value was significantly lower in group 2 compared to group 1, while the Schirmer scores of the groups were similar. Additionally, as DSTCUT increased in group 2, the TBUT value decreased significantly. We considered that STC overuse during the pandemic might affect tear-film evaporation, and might increase the tendency of dry-eye in children. Blue-light exposure of the eyes may be responsible for this situation. One experimental study showed that overexposure to blue light increased the inflammatory markers and reactive oxygen species (ROS) on the ocular surface, disrupted the tear-film content, and thus caused dry-eye (6). In another study, computer workers using digital screens for a long time daily were determined to have worse meibomian gland functions compared to those

Table III. The correlation results between daily smartphone, tablet and computer use time and ocular parameters in group 2

	DSTCUT of group 2	
	r	p-value
Tear beak-up time	-0.368	0.034*
Schirmer test value	-0.265	0.073
Ocular surface disease index score	0.384	0.028*
Spherical equivalent refraction	0.340	0.045*
Axial length	0.296	0.059
Central corneal thickness	0.046	0.795
Keratometry value	0.075	0.592
Anterior chamber depth	-0.161	0.323
Lens thickness	-0.133	0.409
Central retinal nerve fiber layer thickness	0.107	0.568
Central choroidal thickness	-0.263	0.081
Central macular thickness	0.143	0.377

r: Pearson correlation coefficient, *p<0.05 statistically significant
DSTCUT: Daily smartphone, tablet and computer use time

using them for a short time daily (14). Meibomian gland dysfunction might cause a reduction in lipid secretion, an increase in tear evaporation, and thus the development of dry-eye (14,16,17).

In clinical practice, OSDI score is used to show the severity of dry-eye symptoms (10). Moon et al. (12) reported that smartphone use in children caused an increase in their OSDI score. The authors also showed that there was a significant decrease in the OSDI score in children with dry-eye when their smartphone use was discontinued for 4 weeks (12). Computer workers with a daily digital screen time of more than 4 hours were detected to have significantly higher OSDI scores compared to those with the daily digital screen time of 4 hours or less (14). In our study, OSDI score was significantly higher in group 2 compared to group 1. Additionally, as DSTCUT increased in group 2, OSDI score increased significantly. We thought that STC overuse during the pandemic might increase dry-eye complaints in children.

Increased usage of digital screens may play a role in the development of temporary or permanent myopia (18-21). Liu et al. (22) found that children having greater myopic refraction spent more time using computers and smartphones. Myopia development was reported to be more frequent in children with a digital screen contact time of more than 2 hours daily (20). Similarly, Hansen et al. (19) determined that children using digital screens for more than 6 hours daily had a higher risk of developing myopia compared to those using them for less than 2 hours daily. We detected that group 2 had significantly more myopic SER and greater AL compared to group 1. Additionally, as DSTCUT increased in group 2, more myopic SER occurred. In the literature, children spending more time on computers and smartphones were stated to have longer AL (22,23). In children, annual SER changes towards myopia were found between 0.16-0.55 D (24-26), while annual axial elongations were reported between 0.22-0.35 mm (25-27). In our study, annual SER and AL changes during the pandemic were higher than the values reported in the literature, and these increases might be associated with STC overuse. Closer working and excessive accommodation, a higher "accommodative convergence/accommodation" ratio, or peripheral defocus are among the possible mechanisms blamed in the development and progression of myopia due to digital device usage (28). Prolonged digital device usage at a close distance may cause blurred images on the retina due to hyperopic defocus, and the retina may send remodelling signals to the sclera. As a result of this, axial elongation might occur (29).

In our study, CCTs, keratometries, ACDs and LTs of the two groups were similar. Additionally, CCT, keratometry value, ACD and LT were not significantly correlated with DSTCUT in group 2. Therefore, we thought that at 1-year follow-up, STC overuse during the pandemic had no effect on CCT, keratometry value, ACD and LT. Similarly, Liu et al. (22) determined that the values of CCT, ACD and LT were not significantly associated with the time spent on different digital devices. In the literature, there were some concerns that blue light emitted from digital screens might affect the posterior segment structures (7,8). In experimental cell and rat models, it was reported that periodic exposure to smartphone-mimicking low-luminance blue light might cause retinal damage by means of Bcl-2/BAX-dependent apoptosis (7). In another experimental study, it was stated that low-intensity blue light from digital devices, such as monitors and smartphones, might induce ROS production and might cause apoptosis in retinal pigment epithelial cells (8). However, in our study, the RNFL thicknesses of all sections, central, nasal and temporal choroidal thicknesses, and the macular thicknesses of all areas had not changed significantly at 1-year follow-up. Perhaps prolonged STC usage for many years may be necessary for the occurrence of the posterior segment involvement in clinical practice.

Study Limitations

Our study had some limitations. There might be other undetectable additional factors predisposing to dry-eye and myopia or affecting their development. In addition, the children and their parents answering the questionnaire and keeping the timeline might have assumed a relationship between STC usage and ocular findings. Despite these limitations, we believe that this study can provide valuable and comprehensive information about the effects of STC overuse during the COVID-19 pandemic on ocular surface, anterior and posterior segment structures.

Conclusion

In summary, we found that STC overuse during the pandemic might increase the tendency to dry-eye and myopia, and might cause axial elongation. We also determined that at 1-year follow-up, STC overuse had no effect on CCT, keratometry, ACD, LT, and posterior segment parameters. Reducing digital screen contact time during a pandemic may be beneficial in preventing the development or progression of these findings.

Ethics

Ethics Committee Approval: This study was performed with the approval of Tepecik Training and Research Hospital's Medical Research Ethical Committee (approval number: 2020/10-19).

Informed Consent: Written informed consent forms were received from the participants and their parents.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.Ö., B.Ö., Design: H.Ö., B.Ö., Data Collection or Processing: B.Ö., Analysis or Interpretation: H.Ö., B.Ö., Writing: H.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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J Pediatr Res 2021;8(4):498-501
DOI: 10.4274/jpr.galenos.2020.80488

Case Report

The Misdiagnosis and Consequences of the Odontogenic Orocutaneous Fistula by Medical Doctors: A Case Report

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ABSTRACT

It is possible to describe the term fistula as an abnormal connection between different parts of the body. Untreated, specific infections or diseases, chronic infections, congenital deformities, traumatic injuries and postoperative recovery abnormalities may lead to the formation of fistulas. The most common types of oral fistulas can be classified as dentoalveolar, oroantral, oronasal, and orocutaneous fistulas.

Dentists and doctors can frequently misdiagnose odontogenic cutaneous fistulas as cutaneous lesions or non-odontogenic infections. As a consequence of an incorrect diagnosis, it is possible for patients to undergo unneeded and ineffective treatments, such as the surgical excision of the cutaneous lesion, multiple biopsies, and repeated antibiotic administration. It has been observed that misevaluation of the lesion and repeated ineffective interventions can lead to scar formation on the skin, pit defects, hyperpigmentation, and iatrophobia.

In this case report, we aimed to present the follow-up results of a patient with an odontogenic orocutaneous fistula who was misdiagnosed and treated by medical doctors from different branches.

Keywords: Odontogenic cutaneous fistula, endodontic treatment, focal infection

Introduction

It is possible to describe the term fistula as an abnormal connection between different parts of the body. They can be congenital or acquired and also they can also develop in different parts of the body. Specific untreated infections or diseases, chronic infections, congenital deformities, traumatic injuries and postoperative recovery abnormalities may lead to the formation of fistulas. Despite the fact that oronasal, orocutaneous, oroantral and dentoalveolar fistulas are the most frequently observed types because of oral cavity, it is possible for an oral fistula to be dependent on the origin (1).

A pathological pathway between the oral cavity and alveolar bone is known as a dentoalveolar fistula, which generally arises from infected cysts, necrotic teeth, periodontal inflammation, trauma or mandibular or maxillary fractures (2). In the case of a necrotic dental pulp, the root canal develops into a potential site of bacterial colonization. In this case, if it is not treated, the infection spreads into the periradicular area, which leads to apical periodontitis, and follows the path of least resistance in the bone and soft tissue. The direction and site of the fistula to the surface are determined by the location of muscle attachments and the position of root tips. Following the spread of the periradicular infection and the disappearance

***This case report was presented as an oral presentation at the International Dentistry Congress of Erciyes University on 26-29 February 2020.**

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Received: *14.07.2020* **Accepted:** *05.11.2020*

of the cortical wall of the alveolar bone, the fistula follows interstitial spaces. Periradicular infections can reach the oral mucosa or the skin and induce the formation of fistula despite the fact that most of them remain limited within the loose connective tissue compartments and thus lead to the formation of abscess (1).

It is possible to perform a diagnosis by radiographic examination, dental examination, radiologic evaluation, or by placing gutta-percha or similar radiopaque material in the fistula tract. The evidence of the radiolucent periapical disease process is shown by dental periapical or panoramic radiographic images. It is necessary for patients to be assessed by orthopantomography, and if possible, by cone-beam computed tomography. From histological aspects, the cutaneous fistula tract is generally composed of epithelium or granulomatous tissue. Antibiotic therapy, biopsies and multiple surgical excision might be carried out due to diagnostic errors (3). A carious tooth or a history of previous trauma can help diagnose in intraoral examination while evaluating these patients. Nevertheless, dermal lesions are not specific and can also be observed for abscesses, ulcers, cysts and scars (4).

In this case report, we aim to present the dental diagnosis, treatment, and follow-up of a patient with an odontogenic orocutaneous fistula who was misdiagnosed and subsequently attempts were made to treat the patient by medical doctors from different branches.

Case Report

An 11-year-old male patient applied to pediatric dentistry clinic with a complaint of a non-healing wound on his right lower jaw. As a result of the anamnesis taken from the patient, it was determined that he did not have any systemic disease and had undergone three drainage operations on his right lower jaw in the previous year. It was ascertained that he had applied to a paediatric surgery department six months before applying to our clinic, due to periodic discharge under the right chin and redness. He was diagnosed with sebaceous gland inflammation by a paediatric surgeon. The patient was operated on twice by the paediatric surgeon, and it was ascertained that the patient was then referred to a plastic surgeon six months later because of a lack of improvement in the site and aesthetic concerns. The patient was operated on by the plastic surgeon with the diagnosis of sebaceous gland inflammation. Subsequently, the patient was referred to our clinic after the plastic surgeon observed that the discharge was associated with the jaw bone during the operation.

In the clinical examination, the patient had an erythematous extraoral fistula approximately 1 cm in diameter in the lower right area with sutures around it. In tooth 46 of the patient who was thought to have extraoral fistula, a mismatch was observed between the composite resin restoration, cavity wall, and restoration material. Percussion sensitivity was minimum in tooth 46, and intraoral swelling and redness were not observed. In a radiographic examination, an in-depth restoration material and a large periapical lesion were identified in tooth 46.

Root canal treatment was started in the same session in our clinic. Calcium hydroxide dressing was applied and it was filled with temporary restoration material. Two sessions of calcium hydroxide dressing were carried out at two-week intervals. When improvement in the fistula tract was observed in the fourth session, treatment was terminated by filling and root canal treatment (Figure 1).

In the first month check-up of the patient after root canal treatment, a hard, nodular structure was noticeable during palpation at the borders of the site of the surgical operation. The patient was referred to a paediatric unit. As a result of paediatrics consultation, it was determined that there was scar tissue and injections with cortisone content were made in this region. Small plaques of white colour were observed in the scar tissue (Figure 2). The patient was then referred to a plastic surgeon to assess treatment in terms of aesthetic appearance.

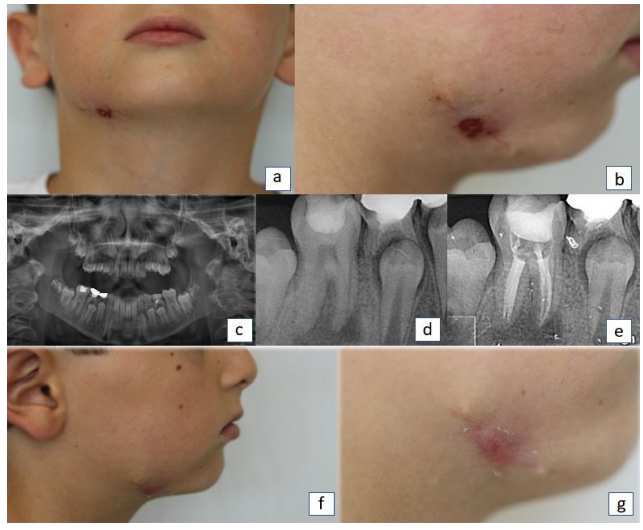

Figure 1. a, b) Preoperative extraoral photograph. c) Preoperative panoramic radiograph of the patient. d) Preoperative periapical radiograph of the patient. e) Postoperative periapical radiograph. f, g) Postoperative extraoral photography

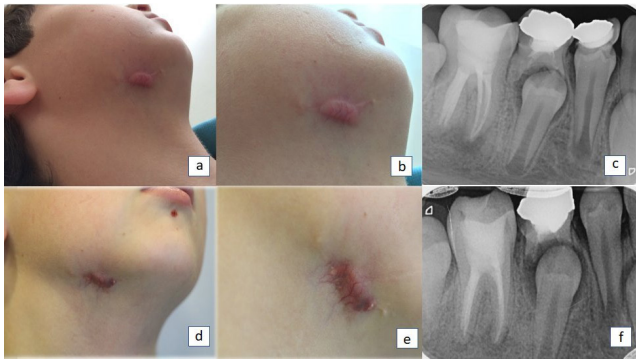

Figure 2. a, b) Extraoral photography of in the first month check-up of the patient after root canal treatment. c) Periapical radiography of in the first month check-up of the patient after root canal treatment. d, e) Extraoral photography of in the third month check-up of the patient after root canal treatment. f) Periapical radiography of in the third month check-up of the patient after root canal treatment

Discussion

The evaluation of the cutaneous fistula tract should begin with a comprehensive history and the awareness that any cutaneous lesion of the face and neck may be of dental origin (5). Patients may complain about dental problems. However, patients may not remember an acute or painful story of onset. With the persistence of a cutaneous lesion, there may also be episodic bleeding or drainage complaints from the cutaneous area. For the correct diagnosis of cutaneous sinus of dental origin, the external appearance of the lesion should be addressed. The most characteristic feature of this type of nodule is depression or withdrawal below the normal surface. This cutaneous retraction or cavitation is caused by the fixation of the fistula to the underlying tissues and may be secondary to the healing process or a late finding inactive disease. Previously biopsied or treated lesions are usually characterized by the absence of at least a portion of the nodule and often with a fistula mouth at the base of the fixed depression (6).

Non-surgical endodontic treatment is often the preferred treatment if the tooth can be restored in cases diagnosed as odontogenic. Extraction is indicated for teeth that cannot be restored (7). The failure of the cutaneous fistula tract to heal after adequate root canal treatment or extraction requires further evaluation, microbiological sampling, and biopsy. In this case report, an 11-year-old paediatric patient was diagnosed with odontogenic orocutaneous fistula of tooth 36 origins, and an improvement was observed only with endodontic treatment. When the age of the patient was considered, it was essential to achieve successful results with endodontic treatment without the need for complex surgical interventions. Surgical operations which were initially performed by medical doctors led to negative aesthetic and psychological results in this paediatric patient.

Systemic antibiotic administration is not recommended in patients with high immune resistance, no systemic signs or symptoms, no prophylactic antibiotic requirement, and with cutaneous fistula tract. The fistula tract provides the drainage of the primary odontogenic area and prevents swelling and pain caused by pressure.

Following a thorough cleaning of the root canal system, the disappearance of the sinus tract generally takes 5 to 14 days (8). From a histological aspect, granulomatous tissue generally covers these tracts. Granulation allows for their healing following the removal of the root canal infection. Occasionally, a shrunken, hyperpigmented, or pink scar is caused by the healing of the fistula tract (8). Hypertrophic scars and keloids are formed as a result of uncontrolled proliferation of fibrous tissue resulting from a deviation in the normal wound healing process following an injury to the skin. Scars can be classified as mature scars, immature scars, keloid scars, hypertrophic scars, and contracture scars if healing results in cutaneous retraction or cavitation. Treatment with cosmetic surgery may be required at a later date. In the case of scar formation, cortisone can be administered. Depending on the administration of cortisone, the storage of the drug under the skin may lead to small white-coloured plaques in the scar tissue. Linear hypertrophic scar formation was observed in this case report. Coloured white plaques were found as a result of cortisone treatment.

The clinician who is to conduct any treatment should consider the possibility of dental origin while diagnosing a cutaneous fistula tract. Consultation based on cooperation is required among doctors (primarily dermatologists), surgeons, and dentists for a comprehensive diagnosis. By means of the identification of the correct nature of the lesion, rapid treatment is simplified, aesthetic problems and patient discomfort are minimized, and the likelihood of further complications is significantly decreased.

It is of critical importance for medical doctors to refer those patients who present with complaints of head and neck abscesses, fistulas, and pain to a dentist with suspected odontogenic infection. Those patients referred to the dentist can be treated in a short time with endodontic root canal treatment or tooth extraction. It was observed that misevaluation of the lesion and repeated ineffective interventions in this case study led to scar formation on the skin, pit defects, hyperpigmentation, and iatrophobia.

Ethics

Informed Consent: The informed consent form was obtained from the parent before the treatment.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.A.Ü., Concept: H.A., Design: H.A., Data Collection or Processing: N.A.Ü., Analysis or Interpretation: H.A., Literature Search: N.A.Ü., Writing: N.A.Ü.,

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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J Pediatr Res 2021;8(4):502-5
DOI: 10.4274/jpr.galenos.2021.79926

Case Report

Congenital Portosystemic Shunt as a Rare Cause of Neonatal Cholestasis: Case Report

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ABSTRACT

Cholestatic jaundice is a complex diagnostic problem with a wide spectrum of possible differential diagnosis in early infancy. We present a case of congenital intrahepatic portosystemic venous shunt as a rare cause of neonatal cholestasis with current treatment recommendations.

Keywords: Portosystemic shunt, neonatal cholestasis, ultrasonography

Introduction

Congenital portosystemic shunts (CPSS) are rare developmental vascular abnormalities with an incidence of about one in 30,000 children (1). These shunts cause a diversion of portal venous flow to the systemic venous system, and thus, splanchnic portal venous blood bypasses the liver parenchyma and various biochemical metabolites (galactose, ammonia, and bile acids etc.) accumulate in the systemic circulation without being metabolized (1). Depending on the accumulated amount of these metabolites, clinical presentation can be quite variable, especially in children. CPSS can either be seen in a symptomatic infant or detected incidentally in a child that undergoes ultrasonography (US) for other reasons. We present a case who underwent abdominal US because of neonatal cholestasis and was diagnosed with CPSS.

Case Report

An 18-day-old male patient presented with a complaint of jaundice which started when he was 3 days old. It was discovered that the patient was born via spontaneous vaginal delivery with a weight of 2,500 gr at the 36th+6 week of gestation from a 27-year-old mother with normal pregnancy period. There was no consanguinity between the parents and there was no history of sibling death. In physical examination, his general condition was good and active, and the patient's body weight was found to be 3,000 gr (3-10th percentile), and his height was 50 cm (10-25th percentile). Sclera and skin were icteric. No evidence of congestive heart failure or hepatosplenomegaly was found.

Laboratory findings were as follows; hemoglobin 12 g/dL mean corpuscular volume 88 fL, leukocyte count 9,100/mm^3, platelet count 185,000/mm^3, serum aspartate transaminase 46 U/L, alanine transaminase 8 U/L, gamma-glutamyltransferase 219 U/L, alkaline phosphatase 126 U/L, total protein 6.1 g/dL, albumin 3.8 g/dL, ammonia 60 µg/dL, total/direct bilirubin 7.3/4.8 mg/dL, phosphorus 3.8 mg/dL. In addition, kidney function tests, serum electrolytes and blood glucose were normal. Arterial blood gas, thyroid function

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Received: *18.11.2020* **Accepted:** *01.01.2021*

test, alpha-1 antitrypsin level, ferritin, complete urinalysis, prothrombin time, activated partial thromboplastin time were normal, and serological examinations for hepatitis A, B and C viruses, cytomegalovirus, Epstein-Barr virus, toxoplasma, rubella and human immunodeficiency virus were negative. In screening for hereditary metabolic disease, the reducing substance in the urine was negative, and urine-blood amino acids and organic acid analysis in the urine by tandem mass spectrophotometer were normal. Blood and urine culture were normal. Echocardiographic evaluation was normal. Eye examination revealed no signs of metabolic disease or cataract. Abdominal ultrasonography was performed for neonatal cholestasis.

In ultrasonography, normal liver contours and parenchymal echo pattern, and parenchymal millimetric rough calcifications in the right subdiaphragmatic area were observed. The gallbladder was normal and no cord sign was noted. Common bile duct and intrahepatic bile ducts were normal. Doppler ultrasonography examination showed that the main portal vein and hepatic artery were normal in diameter and flow pattern. However, the left portal vein diameter was increased and the right portal vein was significantly hypoplastic. Also, there was an aberrant venous connection (3x1.5 mm) between the inferior vena cava and portal vein at the bifurcation level (Figure 1). Hepatic veins showed normal phasic flow and diameter but in the inferior vena cava, there was increased turbulent flow and diameter at the shunt level. There was no evidence of portal hypertension. Liver computed tomography angiography was performed to confirm the findings described on ultrasound and to evaluate other vascular structures, and a single isolated shunt was detected on tomography (Figure 2).

Vitamins A, D, E, K and ursodeoxycholic acid were started as treatment. The patient, who did not develop complications such as portal hypertension, heart failure or hepatopulmonary syndrome during the follow-up, was discharged after 1 week of hospitalization with good activity, nutrition and weight gain. The family was informed about possible complications and called for regular follow-ups. In the check-up ultrasound examination that was performed in the 3rd month, the shunt was completely closed, and band-like linear hyperechogenicity was observed in this area (Figure 1). In addition, the hypoplastic right portal vein diameter was increased compared to the previous examination and the left portal vein diameter had returned to normal (Figure 1). Over time, sclera and skin returned to normal colors and the bilirubin values returned to normal in the sixth month of follow-up. During the whole follow-up,

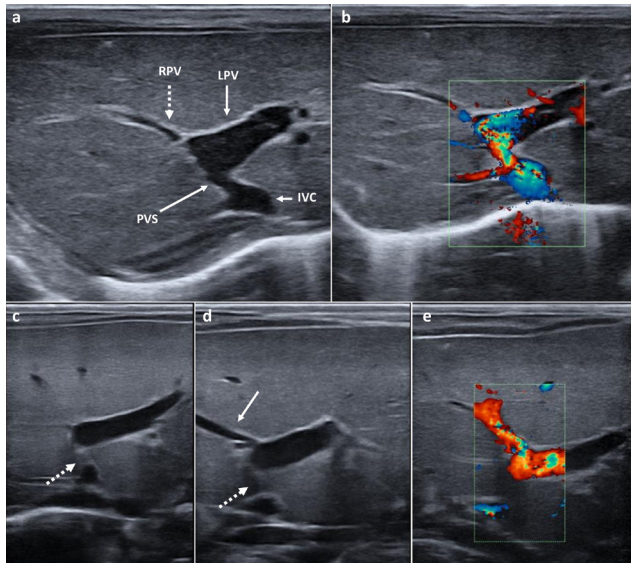

Figure 1. Ultrasound images at the time of diagnosis (a-b) and at third month check-up (c-e). Figure 1a shows the hypoplastic right portal vein (RPV) and the left portal vein (LPV) with increased diameter. Also, porto venous shunt (PVS) is observed between the inferior vena cava (IVC) and the portal vein at the bifurcation level (type 1 CPSS). Figure 1b shows increased turbulent flow and related aliasing artifacts at the shunt level in Doppler ultrasonography. Figure 1c and 1d show the closed shunt (dotted arrow) and linear echogenicities in this area. Gray scale (Figure 1d) and Doppler (Figure 1e) ultrasound images of the right portal vein (straight arrow) shows the increased diameter at the 3rd month check-up, compared to Figure 1a

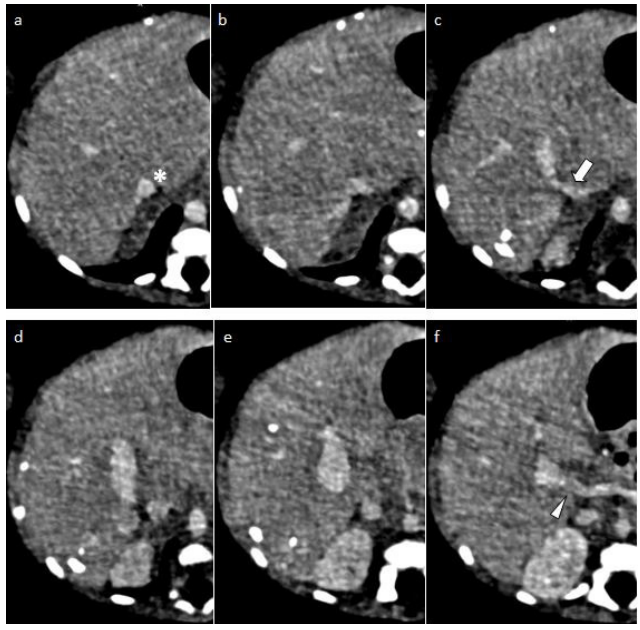

Figure 2. In the axial plane serial images of liver computed tomography angiography; the inferior vena cava (asterisk) is seen in Figure 2a (asterisk) and Figure 2b. Figure 2c shows the shunt extending from the portal bifurcation to the inferior vena cava (white arrow). While enlarged portal bifurcation is observed in Figure 2d and 2e, the main portal vein (arrowhead) observed in normal calibration is seen in Figure 2f

the patient had a lively appearance with normal sleep habits and diet for his age.

The authors declare that informed consent was obtained from the parents for the publication of this case report.

Discussion

CPSS are rare, developmental anatomical abnormalities, resulting in a diversion of portal venous flow to the systemic venous system. CPSS are divided into extrahepatic (abernethy malformation) and intrahepatic types according to their anatomical features (1). Congenital intrahepatic shunts were subdivided into 4 morphological types by Park et al. (2) as follows;

Type 1: a single large shunt connecting the right portal vein to the inferior vena cava

Type 2: a localized peripheral shunt in one hepatic segment where one or more communications are found

Type 3: a communication between the peripheral portal vein and the hepatic veins through a portal vein "aneurysm"

Type 4: multiple and diffuse portosystemic shunts in several segments

CPSS can cause a wide range of clinical symptoms, ranging from asymptomatic patients to those with severe symptoms and complications. Hepatic encephalopathy, pulmonary hypertension, and hepatopulmonary syndrome are the most outstanding symptoms and portosystemic shunt cases can lead to a large extent of metabolic irregularities, while damage to other organs can be seen in a very few cases (3). In the perinatal period, neonatal cholestasis, hyperammonemia, hypoglycemia and hypergalactosemia can occur and should be differentiated from other congenital anomalies such as biliary atresia and accompanying metabolic diseases (4,5).

Due to the wide variability in clinical manifestation, imaging plays a crucial role in the recognition of shunt and accompanied malformations. Doppler ultrasonography is the key imaging modality to show the presence of the shunt and its type. In addition, Doppler ultrasonography can be used to confirm the direction of shunt flow, to calculate the shunt ratio (by dividing the total blood flow volume at the shunt by the total portal vein flow) and for the follow-up of CPSS (6).

Abdominal cross-sectional imaging can provide additional information about the shunt anatomy and characterize any potential focal liver lesion. Although MR angiography can decrease the ionizing radiation exposure especially in pediatric patients, computed tomography angiography is considered the first line screening method (7). This is due to the fact that this method can show even small portosystemic shunt branches properly.

Currently, there is no standard therapeutic approach available for portosystemic shunts which has been adopted for large studies. Treatment options are shaped according to the type of shunt and its clinical course. For those patients with asymptomatic intrahepatic shunts, as is frequently the case in children, follow-up without treatment is recommended. Clinical manifestations are frequently seen in adulthood or in those patients with a shunt ratio greater than 60%; and treatment is recommended at the onset of clinical manifestations (8,9). To date, there is no guide recommending early treatment to prevent undeveloped complications. In those patients with mild clinical signs, intrahepatic small shunts may regress within one year and close spontaneously with a resolution of symptoms (7). Spontaneous closure of intrahepatic shunts often occurs in children with newborn cholestasis, in girls and in those patients with type 4 shunts (10). In contrast to these, extrahepatic shunts and patent ductus venosus are less likely to close (10). It is recommended that all shunts which persist after 1 year of age should be closed regardless of whether complications develop or not (7). The main goal of the treatment is to close the shunt without causing secondary portal hypertension, and shunt occlusion options vary from the least invasive percutaneous endovascular procedures to surgical correction with liver transplantation as a last resort (6).

Intrahepatic portosystemic shunts are unusual vascular anomalies which might be detected as a cause of neonatal cholestasis. This pathology, which can only be diagnosed radiologically, should be on the differential diagnosis list in each examination that is performed for cholestasis. Familiarity with Doppler ultrasonography features of intrahepatic portosystemic shunts could help to diagnose affected patients and to choose the best therapeutic approach.

Ethics

Informed Consent: The authors declare that informed consent was obtained from the parents for publication of the case.

Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

Data Collection or Processing: M.E.P., G.Ö., Analysis or Interpretation: M.E.P., G.Ö., S.Y., Literature Search: C.O., Writing: C.O.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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J Pediatr Res 2021;8(4):506-9
DOI: 10.4274/jpr.galenos.2021.65982

Case Report

A Rare Complication of Insulin Therapy in a Child with Newly Diagnosed Type 1 Diabetes: Insulin Edema

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ABSTRACT

Although insulin therapy has a critical role in the management of patients with type 1 diabetes, it may cause various side effects at varying rates. Insulin edema is a very rare complication that is mostly associated with the initiation of insulin therapy in patients with newly diagnosed diabetes or the intensification of insulin therapy in those with poor glycemic control. Its clinical spectrum ranges from mild peripheral edema to severe serosal effusions (peritoneal, pleural and pericardial) and heart failure. Although it has been known about for a long time, only a small number of cases have been reported on so far and its incidence is not clear. Additionally, most cases are thought to be undiagnosed due to its mild clinical presentation. Here, we present a 10-year-old male with type 1 diabetes who developed insulin edema following insulin therapy and improved spontaneously with fluid/salt restriction. In conclusion, it should be kept in mind that there is a possibility of the development of insulin edema after the initiation of insulin therapy in patients with diabetes.

Keywords: Edema, insulin, type 1 diabetes, ketoacidosis

Introduction

Insulin therapy has a very important role in the management of insulin deficiency. During insulin therapy, various side effects may occur in the short or long term. The most common of these is hypoglycemia and it is known that this can lead to life-threatening consequences. Apart from this well-known side effect, insulin therapy may lead to a rare complication characterized by partial or generalized edema without liver, kidney or heart involvement (1). Although this clinical entity has been known about since the 1920s, it has only been reported on for a small number of cases to date (2). It has been described as a condition which may occur following the initiation or intensification of insulin treatment in children and adolescents with newly diagnosed type 1 diabetes and in adults with poorly controlled type 2 diabetes (3,4). The clinical presentation of insulin edema can range from mild peripheral edema (mostly) to heart failure/serosal edema (very rarely) (4,5). Although various mechanisms thought to cause edema have been proposed, the pathophysiological basis underlying insulin-associated edema has not yet been elucidated (3-5). This condition is transient and often resolves spontaneously without treatment. Here, we present a 10-year-old male with type 1 diabetes who developed insulin edema following insulin therapy and improved spontaneously with fluid/salt restriction.

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Received: *23.02.2021* **Accepted:** *15.03.2021*

Case Report

A 10-year-old male with complaints of weakness, polyuria, polydipsia, and polyphagia for a month, rapid breathing for a week and weight loss (5 kg over 3 months) was admitted to the emergency service. He was born via spontaneous vaginal delivery at term with weight of 3,880 grams. No consanguinity between parents or history of diabetes in his relatives was noted. On physical examination, his weight was 23.9 kg [-0.9 standard deviation score (SDS)], his height was 129 cm (-0.8 SDS), his calculated body mass index (BMI) was 15.02 (-0.7 SDS), his respiratory rate was 43/minute, his body temperature was 36.2 degrees, his blood pressure was 106/72 mmHg, and his skin and mucous membranes were dry. He showed Kussmaul's respiration. In laboratory studies, glucose was 473 mg/dL (60-100), sodium was 132 mmol/L (137-145), potassium was 3.4 mmol/L (3.5-5.5), chloride was 107 mmol/L, urea was 6.6 mg/dL, creatinine was 0.9 mg/dL, venous blood pH was 6.96 and HCO_3 was 6.0 mmol/L (22-26), PCO_2 was 22.9 mmHg (35-45), glycosylated hemoglobin A1c (HbA1c) was 12.9%, and insulin was 0.8 mU/L (N: 2-13). Urine analysis revealed ketonuria and glucosuria. Further laboratory investigations revealed positive anti-islet cell and anti-glutamic acid decarboxylase antibodies. Diabetic ketoacidosis was considered and infusions of 0.1 unit/kg/hour intravenous regular insulin and 3,000 cc/m^2 fluid (consisting of 128 mmol/L sodium, 40 mEq/L potassium and 5% dextrose) were initiated. At the 26th hour of follow-up, as the clinic of ketoacidosis improved, fluid therapy was stopped (a total of 2,890 mL of fluid was given) and intravenous insulin treatment was shifted to subcutaneous regular insulin (1 unit/kg/day). Regular insulin therapy was given for two days, treatment was switched to a combination of glargine and aspart. On the 3rd day of the follow-up, non-tender, pitting edema without skin discoloration developed over the ankles. On the sixth day of his follow-up, his edema extended to the tibiae, periorbital region, scrotum and penis (Figure 1). He did not have respiratory complaints and his other system examinations were normal. His body weight increased to 27.6 kg, blood pressure was 98/56 mmHg, serum sodium was 134 mmol/L, potassium was 3.6 mmol/L, urea was 8.9 mg/dL, creatinine was 0.5 mg/dL, albumin was 3.2 g/dL (decreased from 3.9 gr/dL), blood pH was 7.43, HCO_3 was 25.4 mmol/L, and albuminuria/proteinuria was not detected. Echocardiography, abdominal ultrasonography and chest radiography of the patient were normal. Urine output was 1.4 cc/kg/hour. In this patient whose glucose levels were being regulated with intensive treatment, insulin-associated edema was considered and he was treated conservatively with fluid and salt restriction. The daily total insulin dose was adjusted according to glucose levels and gradually decreased to 0.5 IU/kg/day. When the patient's glucose regulation was achieved and an improvement was observed in the edema, he was discharged. In outpatient follow-ups, it was observed that the edema completely resolved 12 days after the beginning (weight decreased to 25.9 kg, albumin 4.2 gr/dL).

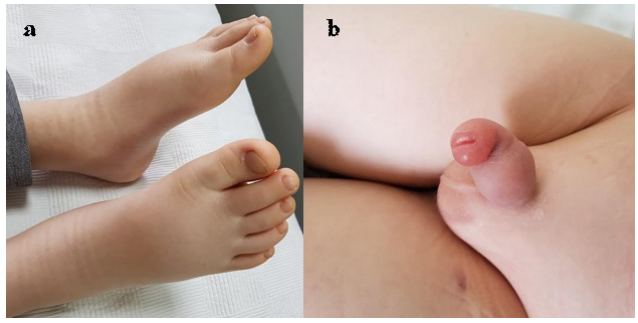

Figure 1. Swelling of the lower extremity (a), scrotum (b), and penis (including the prepuce) (b) on the sixth day of follow-up

Discussion

We present a mild form of insulin edema that occurs after the initiation of insulin treatment and did not cause systemic deterioration in a 10-year-old patient with newly diagnosed type 1 diabetes mellitus. Although this complication has been known about for nearly a century, it has rarely been reported or sometimes may not be recognized (1-3). The diagnosis of this disease, whose incidence is unknown, is based on the exclusion of all other causes (cardiac, renal, etc.) that may lead to edema. Its clinical severity can range from severe serosal effusions and heart failure to mild peripheral edema. Almost all of the cases in which insulin edema was reported in childhood have been newly diagnosed with type 1 diabetes as in our case (1-8). The clinical course of this disease, which is often transient and benign, is self-limited and mostly resolves spontaneously in children or adolescents (4-8). However, it may present with severe clinical manifestations such as pleural effusion and heart failure in elderly patients with pre-existing cardiac diseases (9).

Although the pathophysiology of this disease has not yet been clarified, various mechanisms have been proposed. Leifer (2) suggested that excessive fluid retention in tissues secondary to glycogen accumulation was responsible for the pathophysiology of insulin edema. In the following years, the anti-natriuretic effect of insulin on the diluting segment of distal nephrons was recognized and it has been suggested that it may lead to this clinical picture by altering electrolyte

transport (4,10). Moreover, it was emphasized that insulin can enhance renal sodium absorption (anti-diuretic effect) by stimulating Na+/K+ -ATPase in the proximal tubule and also by increasing expression of Na+/H+ exchanger 3 and thus contributes to the development of this clinical condition (4). Another proposed mechanism to explain fluid retention is inappropriate hyperaldosteronism (11). However, patients with normal serum aldosterone levels have also been reported (7). Apart from these suggested mechanisms, chronic hyperglycemia in these patients has been associated with increased capillary permeability, which leads to the passage of albumin, the major protein constituent of the intravascular space, to interstitial tissues (transcapillary escape of albumin) and an increase of oncotic pressure in the tissues and thus, results in edema (1,4,12). In addition, it is thought that in the catabolic process with insulin deficiency, intensive fluid replacement may cause fluid extravasation to the third space and worsen the clinical picture of edema, which is thought to be similar to the pathophysiology of refeeding edema that occurs after fluid resuscitation in severe malnutrition anorexia nervosa cases (1). The low serum albumin level detected in our case on the day the edema deteriorated suggests the mechanism of transcapillary albumin loss. However, cases without a decrease in serum albumin levels have been reported (4). Having said this, we could not measure serum aldosterone level as seen in most other cases presented. In addition, while female gender and being underweight were predominant in childhood and adolescent cases with insulin edema reported in the literature, our case was male and had normal weight and BMI despite weight loss (4,8).

Insulin edema is a different entity from insulin allergy. Insulin allergy has been reported with a frequency ranging from 0.1% to 3.0% of patients who received insulin therapy (13). IgE-mediated (type 1) reaction is by far the most common type. However, although rare, type 2 or type 4 type reactions have also been reported (13). Clinical findings may occur immediately (type 1) or 2-12 hours after injection (type 3 and 4). In addition, different clinical presentations occur at the injection site depending on the type of reaction. While immediate, erythematous papular, rash and itching are typical findings in type 1, subcutaneous nodules occurring at the injection site, which are formed by different immune mechanisms, are seen in type 3 or type 4. Type 1 is rarely systemic with urticaria, angioedema, or anaphylactic shock (13). On physical examination of our case, however, no clinical condition suggesting allergic reactions was detected and therefore, insulin allergy was ruled out.

Fluid and salt restriction constitute the main treatment approach of insulin edema (1,3,4). This disease has a mild course in most of cases and completely resolves within 1-3 weeks, as in our case, without the need for additional treatment (3,8). In severe decompensated cases (heart failure, serosal effusions), pharmacological treatment may be required (1). Elderly patients with pre-existing renal, hepatic or cardiac disease are at higher risk in this respect. Considering the suggested pathophysiological mechanisms, spironolactone treatment is one of the drugs that can be preferred in cases with inappropriate hyperaldosteronism. In addition, other diuretics are equally effective and safe (1,8).

In conclusion, it should be kept in mind that there is a possibility of the development of insulin edema after the initiation or intensification of insulin therapy in patients with newly diagnosed or previously known diabetes. Although insulin edema usually has a mild clinical condition and can completely resolve spontaneously within a few days or a few weeks, it should be kept in mind that it may lead to severe systemic decompensation such as heart failure and/or serosal effusions in patients with pre-existing heart or renal disease.

Ethics

Informed Consent: Permission was obtained from patients to share their medical information.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.A., Ö.E., Ö.N., Design: S.A., B.Ö., Ö.E., Literature Search: Ö.N., T.K., Bey.Ö., Writing: S.A., B.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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J Pediatr Res 2021;8(4):510-13
DOI: 10.4274/jpr.galenos.2021.64497

Case Report

Total Colonic Tubular Duplication Including Terminal Ileum and Appendix: A Rare Case

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ABSTRACT

Total colonic duplications are rare. This case is reported here in order to discuss the treatment of tubular duplication of the entire colon, appendix and terminal ileum. A 2-year-old girl was admitted with complaints of vomiting, abdomen distension, and defecation difficulty. During laparotomy, a tubular duplication with separate mesentery which had no common intestinal wall was detected at the last 20 cm of the ileum. This duplication continued with a common wall and mesentery from the cecum to the sigmoid colon ending blindly. Resection anastomosis was performed for the completely separated tubular duplication at the terminal ileal segment. The remaining tubular duplication, continuing along the cecum, appendix and colon, could not be resected because of its common mesentery, vascular system, and wide common wall with the normal colon. Colotomy performed at the site of sigmoid colon allowed for the opening of the distal of the cyst to normal colon lumen. Gastrointestinal duplication cysts should be kept in mind in patients with chronic abdominal distension. Surgical treatment methods differ because of the different features and localizations of this tubular duplication.

Keywords: Total colonic tubular duplication, surgical treatment, child

Introduction

Gastrointestinal duplications (GID) are rare congenital anomalies that can be seen anywhere from the mouth to anus (1). It has been reported that their prevalence varies between 1/4,500 to 1/10,000. The colon is involved in only 13% of all duplications, and approximately 250 cases have been cited in the literature (2). 80% of patients have symptoms before 2 years of age (3). While 80% of GIDs have a spherical cystic structure and no connection with the gastrointestinal system, the remaining 20% are tubular in nature and they are associated with the lumen of the normal intestinal tract (4,5). Total colonic tubular duplication also causes severe constipation and distension (6).

In this article, the treatment of a 2-year-old girl with a tubular intestinal duplication that included the terminal ileum, appendix, cecum, ascending colon, transverse colon, descending colon and sigmoid colon is presented in light of the literature.

Case Report

A 2-year-old girl was admitted with the complaints of vomiting, and abdomen distension. She had increasing abdominal distention which had started at the age of one. Her complaints of defecation difficulty and vomiting had begun in the two weeks prior to admission. Physical examination revealed a diffuse abdominal distension. There was an air-fluid level and widespread fecal accumulation was determined on direct abdominal radiography (Figure 1). No pathology was found in the abdominal ultrasonography. Contrast-enhanced abdominal computed tomography (CT) showed dilatation of the small intestine with the normal

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Received: *18.01.2021* **Accepted:** *04.04.2021*

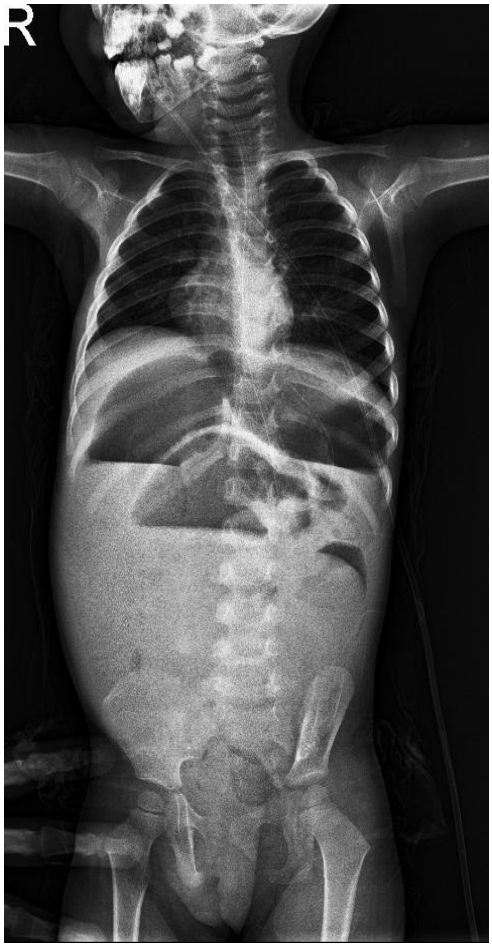

Figure 1. Air-fluid level and widespread fecal accumulation on the direct abdominal radiography

colon (Figure 2). The patient underwent laparotomy due to the absence of regression in the abdominal distension. Dilatation of the small intestines and accumulation of feces were seen. Furthermore, a tubular duplication with separate mesentery which had no common intestinal wall was detected at the last 20 cm of the ileum. This duplication continued along the cecum, appendix, ascending and descending colon and it ended blindly at the rectosigmoid region. The entire colonic tubular duplication, except for the distal ileum, had a common mesentery and a wide common intestinal wall on the antimesenteric surface of the colon (Figure 3). The duplicated lumen on the antimesenteric face was full of feces. It was observed that the initial section of the tubular duplication in the terminal ileum was connected to the actual lumen, and the continuing duplicated lumen ended blindly in the rectosigmoid region. Resection and ileo-ileal anastomosis were performed at the terminal ileal segment for the fully separated ileal duplication. The distal opening part of the duplication continuing with the cecum was closed. The remaining section of this duplication which

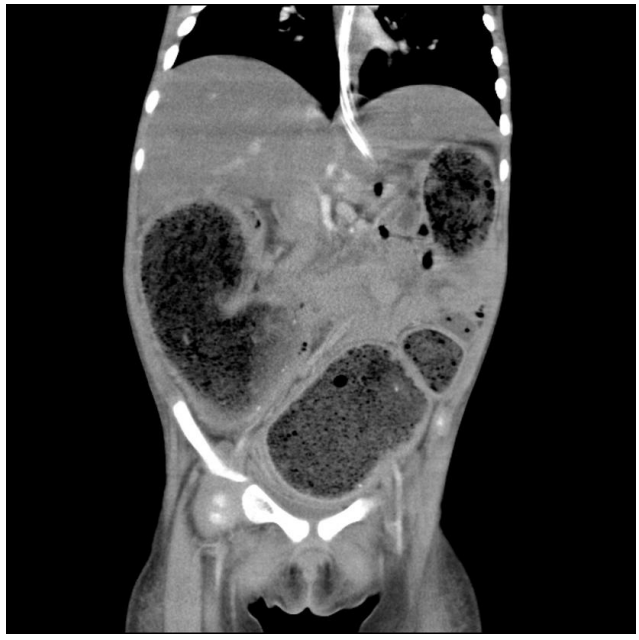

Figure 2. Contrast-enhanced abdominal computed tomography image

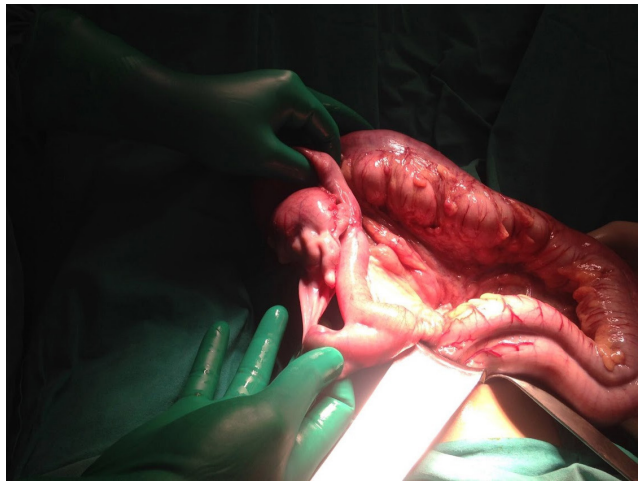

Figure 3. Preoperative image before surgery

continued along the entire colon could not be resected because of its common mesentery and wide common wall with the normal colon. Colotomy performed at the site of the sigmoid colon allowed for the opening of the distal of the tubular duplication to the normal colon lumen. Thus, contrary to the initial anatomy, the proximal opening of the duplex lumen was closed while the luminal opening was provided at the distal end (Figure 4). She did not require any further medical and/or surgical intervention after the operation. She produces stools regularly on a daily basis, and has been growing up without any complaint during 2 years of follow-up. Informed consent was received from the family before the preparation of this manuscript.

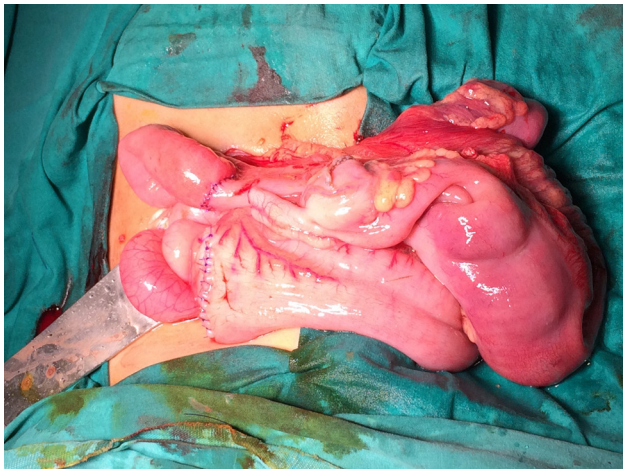

Figure 4. Preoperative image after surgery

Discussion

Although GID can be seen in any age group, they are mostly seen in children younger than two years of age (3,5). The case presented here was in a two-year-old girl.

Colonic duplications are cystic or tubular in nature and constitute 13% of all duplication cysts (2). Tubular colonic duplication can show a function as two perineal anuses in the form of a double-barrelled blind ending, or they can function with a Y-shape as one or two lumen ends blindly such as imperforate anuses in distal (7). The colonic duplication in our case was tubular in nature and Y-shaped, ending blindly in the rectosigmoid junction.

GID contain well-developed smooth muscle in the wall and an epithelial lining resembling some part of the parent bowel (8). In our case, there was no common mesenteric, vascular structure or wall in the tubular duplication of the ileum, whereas the cecum, appendix, ascending colon, descending colon and rectosigmoid region had common mesentery, and a wide common wall with the normal intestine.

Tubular duplications are manifested by symptoms such as constipation, hematochezia, rectal prolapse, fistula, hemorrhoids and abscess according to their location (4,6). Our case had abdominal distension which started at the age of one year and complaints of vomiting and defecation difficulty for two weeks prior to admission. In 15% of patients, multiple duplication cysts can be seen (4). In our case, it was a single duplication, although tubular duplication continued in more than one area of the gastrointestinal system.

Standing direct abdomen radiography, barium imaging examinations, abdomen ultrasonography, CT and magnetic resonance imaging are used to identify duplication cysts (8). Direct abdominal radiography, ultrasonography and CT were used in our case. However, the final diagnosis was made by diagnostic laparotomy.

Esophageal and gastric duplication cysts should be treated with cystectomy and other intestinal cysts should be treated either with cystectomy or resection anastomosis. Cystectomy is sufficient for duplication cysts without lumen connection with the enteric system. In cases where cystectomy is impossible, cystotomy and mucosectomy (Wreen procedure) is an option (9). Although malignant changes are reported in adults with duplication cysts (10), colorectal duplications are benign lesions. Therefore, radical surgical excision is not necessary. Surgical excision in asymptomatic cases is controversial. In addition, resection of the tubular duplicated colon may be impossible due to the presence of common mesentery in most cases (2). In our case, ileal tubular duplication was resected and colotomy performed at the sigmoid colon site in order to open the distal of the tubular colon to the normal colon lumen.

Complications related to surgery are post-operative bleeding, infection and bowel obstruction. However, in patients with total tubular duplication of the entire intestine, short bowel syndrome must be considered after such extensive surgery. Also, there are occasional reports of adenocarcinoma found in duplications, and they are not significantly different between communicating and non-communicating ones. The patient presented here will continue to receive follow-up to determine any possible malignancy.

In conclusion, GID should be kept in mind in patients with chronic abdominal distension and severe constipation. Surgical treatment methods differ due to the different characteristics and localizations of these duplications.

Ethics

Informed Consent: Informed consent was obtained from the parents of the patient for this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.S., T.T., Design: M.S., Ü.B., Data Collection or Processing: M.S, T.T., Ü.B., A.K., Analysis or Interpretation: M.S., T.T., A.K., Literature Search: M.S., Ü.B., Writing: M.S., T.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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J Pediatr Res 2021;8(4):514-6
DOI: 10.4274/jpr.galenos.2021.52297

Case Report

A Preterm Infant with Hypovolemic Shock: Should Infants be Examined Twice or is Once Enough?

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ABSTRACT

Shock in newborns and preterm infants carries significant morbidity and mortality risks unless there is early recognition and adequate treatment. Signs may only be identified in the late decompensated phase with lactic acidosis, cellular disruption, and irreversible multiorgan damage. In neonates, the etiopathological origin is unique, particularly in extremely preterm infants with a complicated postnatal transition phase, an immature myocardium, and high peripheral systemic resistance. Hypovolemic shock shortly after birth is uncommon and may complicate fetomaternal or fetoplacental transfusion, abruptio placenta, intracranial hemorrhage, or capillary leak syndrome. Without a blood loss history, secondary clinical assessment may reveal the underlying etiology and facilitate targeted interventions.

Keywords: Preterm, shock, hypovolemia

Introduction

An extreme preterm female infant was born via cesarean section at 25 weeks of gestation to a 25-year-old primigravida woman. The neonate was resuscitated initially with non-invasive Neopuff positive pressure ventilation and eventually by intubation owing to the poor respiratory drive and bradycardia. The Apgar scores were 3 and 7 at 1 minute and 5 minutes, respectively. The infant was born with a birthweight of 710 g (40th percentile); a length of 31.5 cm (34th percentile); and an occipitofrontal circumference of 21.6 cm (17th percentile). On admission, the infant exhibited swelling in the occipital region, which was identified as caput succedaneum; mild hypotonia; and poor tissue perfusion. Cardiovascular examination revealed normal heart sounds and hyperdynamic precordium. The results of abdominal examination were normal, and no organomegaly was noted. Chest examination showed adequate bilateral air entry and mild subcostal recession on mechanical ventilation support.

Case Report

She was connected to a mechanical ventilator with initial venous blood gas analysis revealing severe metabolic acidosis; pH, 7,001; pCO_2, 6^2 mmHg; HCO_3, 14.6 mmol/L; base excess, -14.8 mmol/L; lactic acid, 10.3 mmol/L; hemoglobin, 9.6 g/dL; glucose, 82 mg/dL; Na, 134 mmol/L; and K, 4.8 mmol/L. The infant's heart rate ranged between 150-180 bpm, and oxygen saturation ranged from 85 to 93% on respiratory support with desaturations, and blood pressure was initially unrecordable. A normal saline bolus was administered, a full sepsis screen was initiated, and the infant was administered ampicillin and gentamicin for presumed sepsis owing to the history of suspected chorioamnionitis. A complete blood cell count revealed a white blood cell (WBC) count of 43,000/µL with 33% polymorphonuclear leucocytes, 21% lymphocytes, 6% monocytes, 5% band neutrophils, 5% metamyelocytes, 3% promyelocytes, 25% myelocytes, 2% blast cells, and 43

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Received: *27.03.2021* **Accepted:** *20.04.2021*

nucleated red blood cells (RBCs) per 100 WBC. A peripheral smear showed anisopoikilocytosis, with normochromic red cells and many nucleated RBCs, neutrophilia with shift to left, and normal platelet count. The Reticulocyte count was 8.2%, and the direct Coombs' test result was negative. The coagulation profile revealed a prolonged prothrombin time and an activated partial thromboplastin time of 17.2 seconds and 110.2 seconds, respectively and an international normalized ratio of 1.6. The basic metabolic panel was normal. Chest and abdominal radiography showed well-expanded lung fields and a normally placed umbilical venous catheter. Emergency packed red cell transfusion of 20 mL/kg was administered considering the severe anemia, and fresh frozen plasma was administered twice for the deranged coagulation profile. Blood pressure improved shortly after the transfusions to a mean of 27-35 mmHg without inotropic support, and the level of lactate gradually declined to normal values during the following days. The patient's hemoglobin concentration increased to 13 g/dL after blood transfusion the following day. Blood culture results were negative; however, C-reactive protein (CRP) tested positive at 17.4 mg/L (normal CRP level <5 mg/L). The infant was successfully extubated to non-invasive respiratory support on day 9 of life and a repeated coagulation profile was normal.

Diagnosis

The low hemoglobin level in the initial blood gas analysis, severe metabolic acidosis, and persistent hypotension alerted the physician to conduct a second clinical assessment to explore signs of possible blood loss. A significant subgaleal hematoma (SGH) was noted in the dependent occipital region of the skull measuring 7×5 cm, which was initially misinterpreted as a caput succedaneum (Figure 1). Brain ultrasonography revealed abundant subgaleal fluid collection with low-level internal echoes and septations measuring at least 5.1×2.6×3.7 cm and representing a large SGH. Brain parenchyma showed bilateral subependymal hemorrhage and mild periventricular flare (Figure 2).

Discussion

SGH is a rare but potentially lethal condition occurring in newborns that typically complicates traumatic delivery, particularly after vacuum extraction or forceps delivery (1). SGH affects approximately 40-60/10,000 deliveries, with a mortality rate of up to 25% of cases (2). Significant blood loss may accumulate between the skull periosteum and the galea aponeurotica secondary to rupture of emissary veins. This unlimited potential space may contain the whole

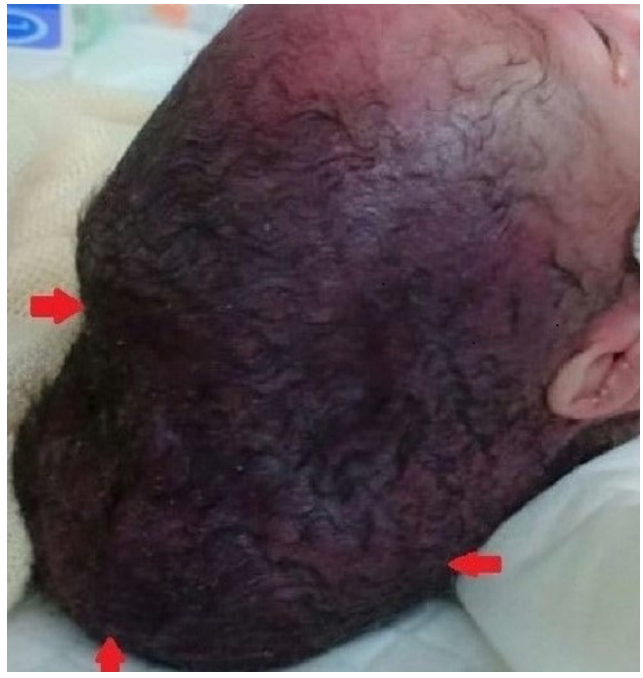

Figure 1. Significant SGH in the dependent occipital region
SGH: Subgaleal hematoma

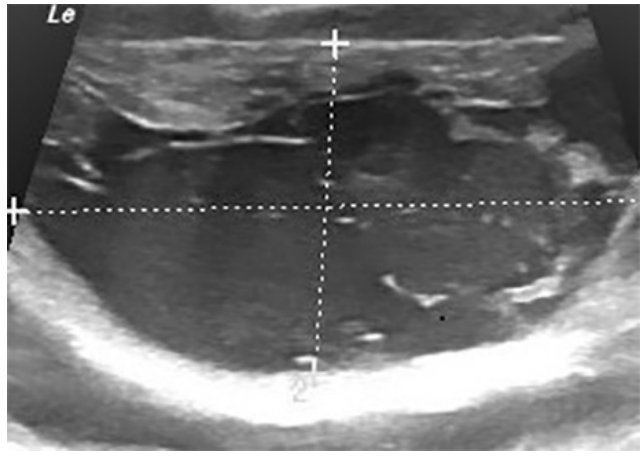

Figure 2. Brain ultrasonography shows large SGH measuring 5.1x2.6x3.7 cm
SGH: Subgaleal hematoma

blood volume of a neonate and result in hypovolemic shock, coagulopathy, and possible death if not promptly recognized (3). Most of the reported cases in the literature involve term infants and this condition is rarely described in preterm infants. To the best of our knowledge, this is the first case report of SGH affecting an extremely preterm infant at 25 weeks of gestation who had not undergone instrumental delivery. A high index of suspicion is warranted for the diagnosis of SGH very early after birth through meticulous physical examination, as this may be lifesaving. SGH may be overlooked during the initial physical examination, and a

second clinical assessment is justified in patients presenting with unexplained hypovolemic shock. Typically, severe SGH may initially mimic caput succedaneum but progresses rapidly as a fluctuant boggy mass crossing all sutures and fontanelles, and causing a significant increase in head circumference (4,5). Early recognition of SGH and prompt commencement of management are key to successful short-and long-term outcome. Close observation of vital signs, serial measurements of head circumference, and monitoring of hematocrit and lactate levels are essential in mild to moderate cases of SGH (6). However, in severe cases presenting with hypovolemic shock, severe anemia, and metabolic acidosis, immediate replacement of volume loss by normal saline boluses, packed RBC transfusions, and possible fresh frozen plasma in cases of coagulopathy are lifesaving (7). A coagulation screen is justified in all cases of SGH, either for diagnostic purposes of a presumed bleeding diathesis as in cases of hemophilia, or for the treatment of the resultant consumption coagulopathy (8). With early recognition and prompt management, the prognosis of SGH is generally favorable, with a notable recent decrease in mortality rates and long-term morbidities (2).

- SGH may be overlooked on initial neonatal examination and a second clinical assessment is justified after admission of infants with severe anemia and/or unexplained hypovolemic shock and increased lactate level.

- Meticulous monitoring and a high index of suspicion are fundamental for the early recognition of SGH that occasionally complicates non-instrumental delivery.

- SGH is a potentially lethal but a preventable clinical emergency and prompt aggressive management definitely improves its prognosis.

Ethics

Informed Consent: The authors certify that they have obtained all appropriate patient consent forms.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.A., A.K., Data Collection or Processing: A.A., A.K., Analysis or Interpretation: A.A., A.K., Literature Search: A.A., A.K., Writing: A.A., A.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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2021 Referee Index

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