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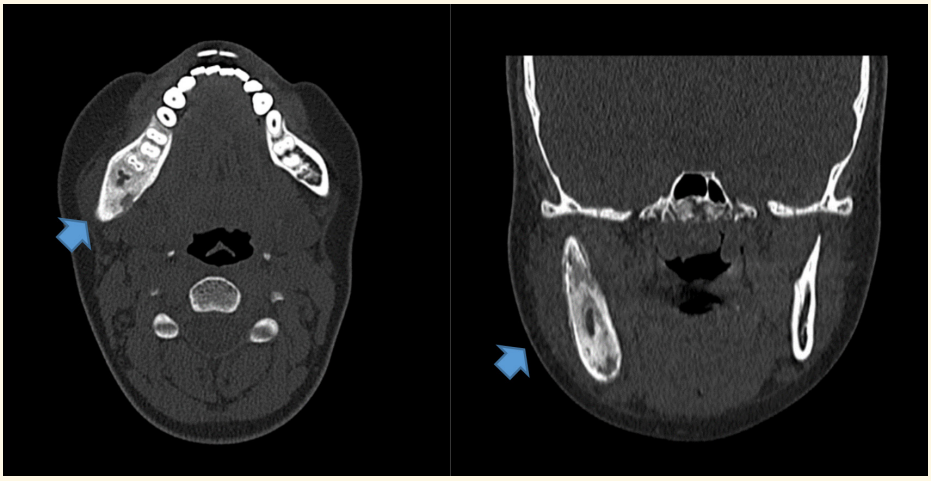

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Aims and Scope

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

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

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

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

Statistical terminology (random, significant, correlation, etc.) should not be used in non-statistical contexts.

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Results: The detailed results of the study should be given, and the statistical significance level should be indicated.

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JPR
The
Journal of Pediatric Research
Official Journal of Ege University Children's Hospital

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Editorial

Dear JPR Readers,

We are pleased to inform you that the new issue of The Journal of Pediatric Research has been published that is indexed in Emerging Sources Citation Index (ESCI), Embase, Directory of Open Access Journals (DOAJ), EBSCO, CINAHL Complete Database, ProQuest, CABI, Gale/Cengage Learning, Ulakbim TR Dizin, TurkMedline, J-GATE, IdealOnline, Hinari, GOALI, ARDI, OARE, AGORA and Türkiye Citation Index.

We present ten articles, including eight original research and two case reports from different disciplines. We hope our reader's interest in reading the article entitled "Severity of childhood asthma among normal, overweight and obese children - a comparative study" from India which can enhance knowledge regarding the effect of metabolic abnormalities on the severity of asthma. Another interesting article is "A Comparison Study in Children with Lower Respiratory Tract Infections: Chest X-Ray and Lung Ultrasound", which can enhance pediatricians' awareness regarding the less harmful diagnostic tool of pneumonia in children. Another article, "Evaluation of Children with Nephrotic Syndrome: Single Center Experience" is a large study, and as the authors mentioned that knowing the demographic, clinical, and pathological features of the disease helps monitor its progress and its prognosis. Our readers can find information about the optimal skin prick test panel for detecting respiratory allergens in children in this issue. Also, this issue covers the alterations in fear and anxiety of Pediatric Dentistry Department admitted children during the COVID-19 pandemic, the impact of a humanoid robot on children's dental anxiety, the spectrum of congenital lung malformations, and prepubertal testicular tumors. Two exciting case reports have been placed on this issue. The first case is a rare malformation of the mandible "Garre's osteomyelitis; the second is encephalitis in an immunocompetent child due to Varicella Zoster Virus. Varicella Zoster Virus is a vaccine-preventable disease emphasizing childhood Vaccines' importance. Pediatricians should enhance the parents' knowledge regarding all vaccine-preventable diseases.

We want to acknowledge the authors, the reviewers, the editorial team, and Galenos Publishing House for their support in preparing this issue. We look forward to your scientific contributions to our future issues.

Assoc. Prof. Dr. Zumrut Sahbudak Bal

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Original Article

Severity of Childhood Asthma Among Normal, Overweight and Obese Children - A Comparative Study

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ABSTRACT

Aim: To determine the severity of asthma among asthmatic children with a) normal body mass index (BMI), b) and those who are overweight or obese. To compare the severity of asthma among children with normal BMI, and those who are overweight and obese.

Materials and Methods: One hundred and fifty asthmatic children meeting the diagnostic criteria were enrolled onto this study. Thorough clinical and anthropometric examinations were carried out. The children were then categorized into two groups based on their BMI as either those with normal BMI or those who were overweight/obese. They were then followed up over 12 months and the information collected was analyzed.

Results: Of the 150 children, 72% were male and 45.3% belonged to the age group of 6-11 years. In 46.7%, asthma was diagnosed <5 years. 50% of the children missed school for between 1 and 5 days per year. The majority (63.3%) of the asthmatic children were able to perform the same level of physical activity as their peers. 54% of the asthmatic children had mild persistent asthma. Overweight/obesity was present in 19.3% of the participants. The majority (72.4%) of the obese asthmatic children were diagnosed <12 years and had moderate-severe persistent asthma. Those asthmatic children who were overweight or obese had more frequent night awakenings and missed more school days at enrolment and during follow-up. The overweight/obese asthmatic children visited the emergency department, required rescue medications and received steroids more often than those children with normal BMI.

Conclusion: Obese asthma is a well-defined phenotype of childhood asthma, characterized by higher disease burden and poor response to treatment. Hence, a two-pronged strategy to tackle being overweight or obese and also to manage the asthma in this group is warranted with strategies directed towards reductions in obesity at an early age in order to help reduce the severity of their asthma.

Keywords: Asthma, BMI, correlation, severity, obesity

Introduction

Asthma is a global health problem with increasing prevalence in most countries, especially among children. The mean prevalence of childhood bronchial asthma among Indian children was 7.24 ± standard deviation 5.42 with a median prevalence of 4.75% (2.65-12.35%) (1). Apart from being the leading cause of hospitalization, it is one of the most important chronic conditions causing elementary school absenteeism (2,3).

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Being overweight or obese have become increasingly common in children around the world (4). Over the past four decades, the mean body mass index (BMI) and obesity rate in the pediatric population have increased significantly worldwide (5). The worldwide prevalence of obesity increased three fold between 1975 and 2016. An estimated 38.2 million children under 5 years of age were overweight or obese in 2019. The prevalence of being overweight or obese rose dramatically from just 4% in 1975 to just over 18% in 2016 among those aged 5-19 (6). The prevalence of obesity among 5- to 19-year-old Indian children ranged between 3.6 and 11.7% (7). The levels of physical activity in this age group have declined due to increased access to various modern conveniences. Besides causing metabolic consequences, obesity, along with a sedentary lifestyle, can affect multiple organ systems within the body negatively including the respiratory system. Of the various complications in patients induced by obesity, asthma is one of the major ones.

Asthma and obesity are growing epidemics in both the developing and the developed world. The prevalence of asthma increases at both extremes of BMI, and findings regarding this have been seen not only in western populations but also in Indian and Chinese children. The significant parallel of increases in the prevalences of obesity and asthma have led to a hypothesis of causality of obesity in development of asthma (8). Obesity has been associated with an increased risk of developing new cases of objectively defined asthma. However; there are conflicting results in the studies available on this subject. Hence, this study was undertaken in order to compare the severity of asthma among normal weight, overweight and obese children.

Materials and Methods

All children aged 1 to 18 years meeting the diagnostic criteria for asthma as per the 2019 Global Initiative for Asthma guidelines were enrolled onto this comparative study after obtaining informed consent from their parents and assent from the children themselves. A detailed history was obtained regarding their age, gender, family history of asthma and obesity, past history, treatment history and symptoms of asthma for the prior 12 months to their enrolment onto this study. A thorough clinical examination including general, systemic and anthropometric examinations was carried out. Their weight was checked using a digital weighing scale with an accuracy of ±100 g. Recumbent length was recorded in children <2 years, using an infantometer, to the nearest 0.1 cm. Height was recorded in older children by means of a stadiometer with an accuracy of ±0.1 cm. BMI was calculated using the formula BMI=weight (kg)/Height squared (m^2). The children were then categorized based on the BMI 2007 World Health Organization reference charts as being obese, overweight or having normal BMI. For this study, the children were classified into two groups i.e. (1) those with normal BMI and (2) those who were overweight/obese. They were followed up for 12 months and their symptom severity was assessed based on their number of exacerbations, their number of emergency department visits, any escalations of their therapy or limitations on their activity. The data were analyzed in order to compare the severity of asthma in the overweight/obese group vs. the normal BMI asthmatic children and to assess the relationship between BMI and the severity of childhood asthma.

Ethical Consideration

Ethical approval was received from the Employees' State Insurance Corporation Medical College and Post Graduate Institue of Medical Sciences and Research Rajajinagar, Bengaluru (approval no: 532/L/11/12/Ethics/ESICMC&PGIMSR/Estt.Vol..IV, date: 15.11.2019).

Statistical Analysis

The information collected was entered into Microsoft Excel and analyzed using SPSS version 21 software. Comparison of variables were calculated by using chi-squared test. Values of $p<0.05$ were considered as statistically significant.

Results

Of the 150 asthmatic children enrolled in this study, the majority (72%) were male. Most children belonged to the age group of 6-11 years (45.3%), followed in decreasing order of frequency by children aged ≥12 years (49%) and ≤5 years (33%), as seen in Table I.

Family history of asthma was present in 44% of the children. Among those who had a positive family history, 12.7%, 6.7% and 5.3% had a history of treated or untreated asthma in their mother, father and brother, respectively.

Table I. Age and sex distribution

Age and sex	Number	%
≤5 years	33	22
6-11 years	68	45.3
≥12 years	49	32.7
Male	108	72
Female	42	28

Forty-six percent of the asthmatic children in our study were diagnosed with asthma before 5 years of age, while 42% and 11.3% of the asthmatic children were diagnosed between 6-11 years and after 12 years of age, respectively (Table II).

Forty-six percent of the children were on controller medications prior to enrolment. Of these, 94.2% received inhaled medications (Table III).

Over the 12 months preceding enrollment into this study, the majority of the children missed school due to symptomatic asthma with 49.3% and 38% having missed 1-5 school days and 6-10 school days in the previous year, respectively (Table IV). 55.3%, 25.3% and 17.3% of the children had visited the emergency room for symptoms of asthma once, twice or 3 or more times respectively. 44.7% of the children had received rescue medications >2 days per week, and 40.7% and 12.7% of the asthmatic children had used rescue medications ≤2 days per week or daily, respectively, while 2% of the children reported no use of any rescue medications. 45.3% of the asthmatic children had received oral or intravenous steroids during acute exacerbations.

Table II. Age at first diagnosis

Age at first diagnosis (years)	Number	%
≤5	70	46.7
6-11	63	42
≥12	17	11.3

Table III. Medication history

(n=150)		Number	%
On medications	Yes	69	46
	No	81	54
Inhaled/Oral	Inhaled	65	94.2
	Oral	4	5.8

Among the study participants, 54.7%. 21.3%, 22.7% and 1.3% had mild persistent asthma, moderate persistent asthma, intermittent asthma or severe persistent asthma, respectively (Figure 1).

The majority of the asthmatic children in the present study had a normal BMI. However, 19.3% of the asthmatic children were overweight or obese.

Breathlessness and chest tightness were more often seen in those asthmatic children who were overweight or obese than in those with normal BMI (p<0.05) (Table V).

When compared to those children with normal BMI, a higher number of overweight/obese children had moderate

Table IV. School absenteeism

Missed school days in a year	At enrolment	
	Number	%
1-5 days	74	49.3
6-10 days	57	38
≥11 days	4	2.7
None	15	10

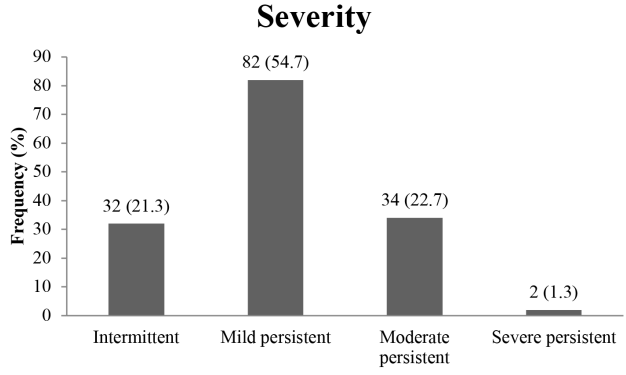

Figure 1. Severity of asthma

Table V. Frequency of symptoms among the two groups

		Normal BMI		Overweight/Obese		p-value
		n	%	n	%	
Cough	Yes	96	79.3	20	69.0	0.231
	No	25	20.7	9	31.0	
Breathlessness	Yes	17	14.0	12	41.4	0.001*
	No	104	86.0	17	58.6	
Chest tightness	Yes	5	4.1	6	20.7	0.006*
	No	116	95.9	23	79.3	
Wheezing	Yes	42	34.7	2	6.9	0.003*
	No	79	65.3	27	93.1	

*P-value of <0.05, i.e., a value of significance.
BMI: Body mass index

Table VI. Comparison of the treatment of exacerbations among the two groups

At enrolment		Normal BMI		Overweight/Obese		Likelihood ratio	p-value
		n	%	n	%		
Emergency room visits	1 time	66	54.5	17	58.6	1,903	0.593
	2 times	32	26.4	6	20.7		
	≥3 times	20	16.5	6	20.7		
	None	3	2.5	0	0.0		
Rescue medicine used	≤2 days/week	55	45.5	6	20.7	8,002	0.046
	>2 days/week	52	43.0	15	51.7		
	Daily	12	9.9	7	24.1		
	None	2	1.7	1	3.4		
Steroids received	1-2 times	48	39.7	17	58.6	4,134	0.127
	3-4 times	2	1.7	1	3.4		
	None	71	58.7	11	37.9		

BMI: Body mass index

persistent asthma (44.8% vs. 17.4%) or severe persistent asthma (3.4% vs. 0.8%) with p=0.015.

Asthmatic children who were overweight/obese had more frequent night awakenings and a higher number of missed school days (p=0.005). The level of physical activity was less in those with higher BMI compared to those with normal BMI (54% vs. 32%), however this was not statistically significant (p=0.63).

When the treatment received for exacerbations prior to enrolment was compared among the two groups, it was found that there was a significant association between being overweight/obese and the use of rescue medication (p=0.046) (Table VI).

Asthmatic children who were overweight/obese had significantly higher numbers of night awakenings, school absenteeism, emergency department visits, need for rescue medications for symptom control and steroid use when compared to those asthmatic children with normal BMI on follow-up (p<0.005).

Discussion

The association between obesity and asthma has been a topic of much interest owing to the rising prevalence of both these chronic health conditions among the pediatric population across the globe. Mechanisms which might explain this association include lower lung volumes due to increased weight on the chest wall and/or pro-inflammatory mediators released by adipocytes (9,10).

The present study was undertaken in order to compare the severity of asthma among children with normal BMI vs. those who were overweight/obese among 150 asthmatic children aged 1-18 years. The majority (n=108, 72%) of the asthmatic children in this study were male and the most common age group was 6-11 years (45.3%), which is similar to the findings noted in the study by Gürkan et al. (3).

Most children in the present study were diagnosed with asthma before 5 years of age (46.7%). This supports the observation made by Radhakrishnan et al. (11) who examined trends in the age at diagnosis of asthma in eight consecutive birth cohorts and found that there was a steady decline in the age of diagnosis from 4.7±1.5 years in the year 1993 to 2.6±2.0 years in 2000.

Asthma is an important cause of school absenteeism. As many as 90% of the children in the present study missed school for one or more days due to symptoms of asthma, with most children having missed 1-5 school days in a year (49.3%). Meng et al. (12) in their study on asthma related school absenteeism found that 23% of the asthmatic children aged 4-17 years missed school for at least 1 day per year.

The levels of physical activity of the asthma sufferers when compared to their peers was relatively unaffected in most asthmatic children in the present study. The majority (63.3%) of children reported the ability to perform at the same level of physical activity as their peers, a finding consistent with that of the study by Nystad (13) who concluded that asthmatic children in their study were as physically active as their peers.

Before enrolment into this study, 52% of the children had been hospitalized for asthma exacerbation once and 8%

of the children had had more than one hospital admission. Gürkan et al. (3) noted that, of the 140 children in their study, 30 (21.4%) had more than one admission per year.

The prevalence of being overweight/obese among asthmatic children was 19.3%. This was similar to the finding by Chen et al. (14) who found a 19.7% prevalence of obesity among asthmatic children.

When the treatments received for exacerbations prior to enrolment were compared among the two groups, it was found that there was a significant association between being overweight/obese and the use of rescue medication (p=0.046), as was also observed by Lang et al. (15) who found that overweight/obese children had three times more frequent use of rescue treatment than normal weight children.

Overweight/obese asthmatic children visited the emergency department, required rescue medications for symptom control and received steroids more often than children with normal BMI. Quinto et al. (16) observed that overweight/obese asthmatic children had higher oral corticosteroid use than those children with normal BMI.

Study Limitations

This was a single center study. And the sample size was small.

Conclusion

Obese asthma is a well-defined phenotype of childhood asthma characterized by higher disease burden and poor response to treatment. Hence, a two-pronged strategy to tackle being overweight/obese and to manage asthma in this group is warranted. Children with asthma who are overweight/obese have a higher number of emergency room visits, hospitalizations and a greater use of rescue medications and steroids. Hence, strategies directed towards the reduction of obesity at an early age may help to reduce the severity of asthma.

Ethics

Ethics Committee Approval: Ethical approval was received from the Employees' State Insurance Corporation Medical College and Post Graduate Institue of Medical Sciences and Research Rajajinagar, Bengaluru (approval no: 532/L/11/12/Ethics/ESICMC&PGIMSR/Estt.Vol..IV, date: 15.11.2019).

Informed Consent: The informed consent was obtained from their parents and assent from the children themselves.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: N.U.R., P.K., Design: N.U.R., P.K., Data Collection or Processing: N.U.R., V.S.B., Analysis or Interpretation: N.U.R., V.S.B., Literature Search: N.U.R., P.K., Writing: N.U.R., V.S.B.

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Original Article

A Comparison Study in Children with Lower Respiratory Tract Infections: Chest X-ray and Lung Ultrasound

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ABSTRACT

Aim: Lower respiratory tract infections (LRTIs) are one of the leading causes of mortality and morbidity in children. Chest X-rays, which are frequently used in diagnosis, cause ionizing radiation exposure and a loss of time. We aimed to compare the diagnostic accuracy of chest radiography (CR) and lung ultrasonography (US) in patients with LRTIs.

Materials and Methods: This study was designed as methodological research. Of the 62 patients evaluated in our study, four refused to participate, and eight were excluded from the study due to their underlying chronic diseases. All 50 remaining patients (between the ages of 0-18 years) were evaluated with a preliminary LRTI diagnosis. Lung US was performed by a 3rd-year pediatric resident who had six hours of online US training. CR was taken after lung US.

Results: The mean age of the 50 cases included in this study was five years and three months; 35 of the 50 patients (70%) had a clinical diagnosis of pneumonia, 15 (30%) of them had a clinical diagnosis of bronchiolitis. Statistically significant interobserver agreement was found between US and CR [Kappa value 0.772, 95% confidence interval (0.590-0.925) (p=0.000)]. The sensitivity of lung US was 95%, and its specificity was 85.7% when CR was accepted as the gold standard.

Conclusion: Our study demonstrates that lung US can be used instead of CR to diagnose and follow-up pediatric cases with LRTIs.

Keywords: Pediatric emergency medicine, pneumonia, lung ultrasonography, chest radiography

Introduction

Lower respiratory tract infections (LRTIs) are one of the leading causes of mortality and morbidity in children worldwide (1). Chest radiography (CR) is the standard diagnostic method in children with LRTI and it is frequently used. This situation causes potential complications due to ionizing radiation exposure, a loss of time, and unnecessary antibiotic use in children. Therefore, in recent years, many quality improvement methods suggest limiting the use of X-rays in pediatric patients (2).

With the application of bedside lung ultrasonography (US) in the pediatric emergency department, we propose a faster, cost-efficient, repeatable, portable, and radiation-free method for diagnosis. A pediatric resident who had

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no previous US experience performed lung US after a six-hour online US training course. We aimed to compare the diagnostic accuracy between CR and ultrasonographic evaluations of lungs in patients with a preliminary diagnosis of LRTI.

US has significant advantages over CR and computed tomography (CT), such as real-time imaging, accessibility, its portability and suitability for bedside use, the elimination of radiation exposure, and the fact that it does not require the use of contrast materials (3). With the developments in US technology and increased scientific evidence in recent years, the use of lung US has gradually expanded. US has been called "the visual stethoscope of the 21st century" (4). US has been accepted as a good bedside "gold standard" method in critically ill patients (5). The upper and lower points on both hemithorax and the posterolateral alveolar/pleural syndrome points are evaluated by using the Bedside Lung Ultrasound in Emergency (BLUE) protocol, which is a method for diagnosing acute respiratory failure (5). The BLUE protocol algorithm defines normal lung, pleural effusion, consolidation, interstitial syndrome, and pneumothorax conditions. In this protocol, it is recommended to evaluate critical lung pathologies by considering gravity, assessing the pleural line, determining lung sliding findings from the standard points, interpreting artifacts, and considering that many essential pathologies of the lungs are superficial (5-7).

Materials and Methods

This study was designed as a single-center, prospective methodological study. The families of the patients' who participated were informed about the research and agreed to sign consent forms. Those patients diagnosed with LRTI and who were scheduled to have chest X-ray by the pediatric emergency physician were included in this study. Sixty-two patients (0-18 years) were admitted to the pediatric emergency department between 10/1/2020 and 4/1/2021. Out of these 62 patients, eight were excluded because of their chronic lung diseases, and four were excluded because they chose not to participate. Therefore, 50 patients prospectively participated in our study. Lung US was performed by a medical doctor who had graduated from a 6-year medical school and was a 3rd year pediatric resident (pediatric residency is a four-year program in our country, Turkey), and who had received six hours of online US training but had no previous US experience. The six-hours training course consisted of four hours of theoretical and two hours of practical training.

In terms of the standardization of ultrasonographic evaluation, the BLUE protocol was used. Lung US imaging was performed from the BLUE points in both hemithorax for each patient. The inclusion criteria were being aged between 0-18 years, having a clinical diagnosis of LRTI (The American Academy of Pediatrics criteria were taken as the basis for the clinical diagnosis), and a signed patient consent form. The exclusion criteria were specified as follows: The presence of a chronic lung disease (asthma, cystic fibrosis, bronchiectasis) and/or morbid obesity. All sonographic examinations were performed using a standard US device (Mindray DC-60 Expwith X-Insight) with a linear 13-3 and a convex 6-2 probe. The US images obtained by using the BLUE protocol were recorded. The patients' ages, gender, underlying diseases, complaints, physical examinations and laboratory findings, clinical diagnoses, and respiratory support status were recorded on a study form. US evaluation was performed by a pediatric resident regardless of other imaging tests; the presence of lung consolidation, subpleural consolidation, pleural effusion, A-lines, and B-lines were examined. In addition, specific accompanying sonographic findings were noted on the study form. The pediatric resident who performed lung US did not see the results of the CR. The CR was taken after the lung US. The CR images of the patients were evaluated by the radiology physician independently and without knowledge of the different imaging methods and the US results available in the system. Ethical approval was received from the Ethics Committee of Manisa Celal Bayar University Medical Faculty of Health Sciences (decision no: 108, date: 21.09.2020). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Statistical Analysis

The Statistical Package for the Social Sciences version 22.0 package program was used for the data analysis. Numbers and percentages are specified as descriptive statistical data (mean, standard deviation, minimum, maximum, median). Minimum and maximum values are specified as categorical variables, and mean values are given for numerical variables. The McNemar-Bowker chi-squared test was used to analyze categorical variables and evaluate diagnostic accuracy, and Kappa statistics were calculated. A value of $p<0.05$ was considered statistically significant in all analyses.

Results

Of the 62 patients evaluated in our study, four declined to participate, and eight were excluded from the study due to their underlying chronic diseases. Fifty patients

were included in the final analysis. The clinical diagnosis was pneumonia in 35 (70%) patients and bronchiolitis in 15 (30%) patients (Figure 1) (The criteria of the American Academy of Pediatrics were taken as a basis for the clinical diagnoses).

The mean age of the patients was 63.6 months (3-204 months) with a male predominance (54%). The most frequent symptom on admission was cough (54%), followed by dyspnea (46%), fever (44%), rhinorrhea (26%), and fatigue (20%) (Table I). Physical examination revealed rales (52%), rhonchus (42%), tachypnea (28%), retraction (28%), and tachycardia (22%). The mean values of the laboratory parameters were as follow; white blood cell: 12,270 /mm^3, absolute neutrophil count: 7,810 /mm^3, absolute lymphocyte count: 3,450 /mm^3, hemoglobin: 11.8 g/dL, platelet: 299,000/mm^3, C-reactive protein (CRP): 17.19 mg/L, procalcitonin: 6.35 ng/mL, and lactate: 1.74 mmol/L. The most common oxygen therapy methods were simple mask (16%) and high-flow nasal cannula oxygen therapy (16%), followed by mechanical ventilation (6%) and non-invasive ventilation (2%). The remaining thirty (60%) patients did not require oxygen (Table I).

Table I. Patient demographics and clinical information

Patient characteristics	**n (%)***
Age (mean) (min.-max., ±SD)	5.38 (0.25-17.0) (±5.26)
Male	27 (54)
Complaints on admission	
Fever	22 (44)
Cough	27 (54)
Dyspnea	23 (46)
Rhinorrhea	13 (26)
Fatigue	10 (20)
Physical examination findings	
Rales	26 (52)
Rhoncus	21 (42)
Tachypnea	14 (28)
Retraction	14 (28)
Tachycardia	11 (22)
O_2 therapy methods	
Room air	30 (60)
Simple mask	8 (16)
HFNC	8 (16)
NIV	1 (2)
MV	3 (6)

*Unless otherwise specified
min.-max.: Minimum-maximum, SD: Standard deviation, NIV: Non-invasive ventilation, MV: Mechanical ventilation, HFNC: High-flow nasal cannula

The US revealed infiltration in 46% of the patients, hyperinflation in 4%, and no abnormality in 50%. CR showed infiltration in 40% of the patients, hyperinflation in 2% of the patients, and normality in 58%. US findings were inconsistent in 5 patients (4 infiltrations, one hyperinflation), whereas no abnormality was detected via CR. CR revealed infiltration in 1 patient, whereas US showed no pathological finding.

A statistically significant correlation was found between US and CR [Kappa value 0.772, 95% confidence interval (0.590-0.925) (p=0.000)]. The sensitivity of the US was 95%, its specificity was 85.7%, its positive predictive value was 82.6%, and its negative predictive value was 96% when the patients with hyperinflation were excluded and CR was accepted as the gold standard (Table II).

Discussion

One of the most appropriate definitions for the diagnosis of pneumonia in primary health care settings in children is the definition of the World Health Organization (WHO). The WHO defines pneumonia as the clinical picture, with fever not associated with another cause, and accompanying tachypnea, cough, and respiratory distress. The purpose of this definition is to facilitate access to life-saving antibiotics in underdeveloped countries with a very high incidence of pneumonia, however, it is not a specific definition (8).

In our study, the complaints of the cases were cough which was the most common (54%), dyspnea (46%), fever

Table II. Sensitivity, specificity, positive predictive value, and negative predictive value of lung ultrasonography vs chest radiography in diagnosing LRTI. The two patients with hyperinflation in US imaging were excluded and CR was accepted as the gold standard (n=48)

	US		**Se (%)**	**Sp (%)**	**PPV (%)**	**NPV (%)**
CR	**Negative**	**Positive**	**(95% CI*)**	**(95% CI*)**	**(95% CI*)**	**(95% CI*)**
Negative	24	4	95	85.7	82.6	96
Positive	1	19	(75.13-99.87)	(67.33-95.97)	(65.59-92.21)	(77.93-99.39)

*CI: Confidence interval, Se: Sensitivity, Sp: Specificity, PPV: Positive predictive value, NPV: Negative predictive value, US: Ultrasonography, CR: Chest radiography, LRTI: Lower respiratory tract infection

(38 °C and above) (44%), rhinorrhea (26%), and fatigue (20%). Compared to the literature, the rates of admission with fever and cough were found less commonly in our study (9-11). This difference may be due to the inclusion of all LRTI cases clinically diagnosed with pneumonia and bronchiolitis in our study. In addition, unlike other studies, outpatients were included in this study.

The most common findings were rales, rhonchus, tachypnea, retraction, and tachycardia. In our study, similar to the literature, the elevation of acute phase reactants such as CRP and procalcitonin correlated with the physical examinations and imaging findings of those patients with suspected bacterial pneumonia (12-15). Respiratory support requirement was less common in our study when compared to the literature (10,16,17). This lower rate could be due to our study's inclusion of outpatients.

In our study, 3 cases (6%) with a pleural effusion of 15 mm or more were detected via US, whereas they were evaluated as normal by CR. The US was performed by an experienced radiologist who confirmed the presence of effusion. US was found to be more sensitive than CR in detecting effusion. Esposito et al. (18) conducted a study comparing the diagnostic values of US and CR; US was found to be more effective in detecting pleural effusion, which supports our results. The findings of this study confirm that lung US is an imaging technique which is almost as reliable as CR in identifying lung lesions diagnostic for LRTI and they show that it is even more effective than CR in diagnosing pleural effusion. When CR is accepted as the gold standard, the sensitivity of lung US was 95%, and its specificity was 85.7%. In the study conducted by Reissig et al. (19), infiltration, air bronchogram, pleural effusion, and pleural irregularities were detected by lung US. It was shown that the diagnosis of pneumonia was made with a sensitivity of 93.4% and a specificity of 97.7% (19). A meta-analysis by Pereda et al. (20) evaluated the accuracy of US in the diagnosis of pneumonia in pediatric patients and it showed that US was successful in diagnosing pneumonia with 96% sensitivity and 93% specificity.

Copetti and Cattarossi (21) compared the diagnostic values of CR and US in 79 children with pneumonia, and US detected pneumonia in 60 out of 79 patients. In contrast, positive CR findings were observed in only 53 patients. CT confirmed the diagnosis of pneumonia in 4 patients found to be negative on CR and positive on US (21). Esposito et al. (18) compared the diagnostic values of US and CR and showed that US had 98% sensitivity and 95% specificity (19). The sensitivity rate in our study was consistent with results in the literature, and the specificity rate was slightly lower (19-21). This result occurred because four false-positive cases were detected in the US evaluation when CR was taken as the reference test. However, pleural effusion was detected sonographically in 3 out of 4 cases where the US detected pathology, but CR was evaluated as normal. This was confirmed when an experienced radiologist performed the US.

Adult studies suggest performing thorax CT if US detects any abnormality, even if CR is normal. Parlamento et al. (22) evaluated adult patients who were positive in US and negative in CR; CT confirmed the positive US results. In the diagnosis of pneumonia, US has been assessed to be a fast, reliable, non-invasive bedside technique. Since CR and US are not the gold standards in adult patients, their sensitivity and specificity could not be specified as CT cannot be applied to every patient, although it is the gold standard (22). We try to avoid radiation exposure in the pediatric age group. Therefore, we did not perform CT to confirm the diagnoses.

Study Limitations

The most important limitation of our study was the low number of patients. Our study, which was carried out during the COVID-19 pandemic, was affected by reduced admissions to the pediatric emergency department. In addition, the increased use of personal protective equipment and isolation methods, such as the closure of schools during the pandemic period, reduced the frequency of admissions to the pediatric emergency service due to LRTI. Another limitation of our study was that, as in other studies evaluating the role of lung US in diagnosing LRTI in children, thoracic CT could not be performed ethically on pediatric cases. Therefore, no comparison with CT, which is reliable in diagnosis, could be made.

Conclusion

Our study demonstrated that lung US can be used instead of CR in the diagnosis and follow-up of pediatric LRTI. This study, carried out after a six-hour online lung US course by a pediatric resident who had no previous US experience, showed that the diagnostic accuracy between US evaluation and CR, even with just six hours of training, was significantly consistent. As a result of a literature review, we determined that this was the first study conducted by a pediatric resident after an online lung US training course.

Ethics

Ethics Committee Approval: Ethical approval was received from the Ethics Committee of Manisa Celal Bayar University Medical Faculty of Health Sciences (decision no: 108, date: 21.09.2020).

Informed Consent: The families of the patients' who participated were informed about the research and agreed to sign consent forms.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.G., Concept: N.G., A.B., Design: N.G., A.B., Data Collection or Processing: N.G., N.C.K., F.D., Analysis or Interpretation: N.Z., F.D., A.B., Literature Search: N.G., N.C.K., Writing: N.Z., A.B.

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

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Original Article

Prepubertal Testicular Tumors in Children: Single Center 17 Years Experience

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ABSTRACT

Aim: Testicular tumors are rare in children and have a bimodal distribution. The first peak is at two years of age in boys and comprises mainly non-GCNIS derived tumors (pre-pubertal teratoma and yolk sac lesions). Here, the clinical features and treatment of testicular tumors in pre-pubertal children in our center are presented.

Materials and Methods: The clinical records of those patients treated for testicular tumors younger than 18 years in our institution from January, 2006 to June, 2022 were reviewed retrospectively.

Results: A total of 12 patients were included in this study. All of the patients were younger than 3 years, except for one patient, who was 8 years old. The median age at primary diagnosis was 17 months (1-107 months). The most common clinical presentation was testicular swelling (n=9). Three patients were diagnosed incidentally. Serum α-fetoprotein (AFP) was increased in 3 patients with yolk sac tumors (>1,000 ng/dL) and in one patient with mature cystic teratoma (1 month-old infant with an AFP concentration of 629 ng/dL). Preoperative β-hCG levels were normal in all patients (<1.2 mIU/mL). Of the 11 patients whose preoperative scrotal ultrasound could be obtained, 5 solid-cystic lesions, 3 cystic lesions, and 2 solid lesions were reported. Calcification was detected in 4 patients. All 4 patients with malignant tumors and 3 patients with benign tumors underwent radical inguinal orchiectomy. Of the 5 tumors removed by testis preserving surgery, 2 were mature teratomas, 2 were epidermoid cyst and 1 was a benign multi-cystic lesion. There was a patient with yolk sac tumor who died in the fifth month postoperatively while receiving chemotherapy. The remaining patients had no metastatic or local primary testicular tumor recurrence during a mean follow-up of 92 months (2-198 months).

Conclusion: Most pre-pubertal tumors are benign and testicular sparing surgery can be performed in patients with negative serum tumor markers. Inguinal radical orchiectomy is sufficient in the treatment of yolk sac tumor.

Keywords: Child, orchiectomy, organ sparing treatments, testicular germ cell tumor, testicular neoplasms

Introduction

Testicular tumors in children are very rare lesions. These tumors represent 1-2% of all pediatric solid neoplasms with an incidence of 0.5-2 per 100,000 children (1,2). Pediatric testicular tumors have a bimodal distribution. The first peak is at two years of age in boys, and the second peak is seen after puberty (3).

Primary testicular tumors have been categorized into two main groups in the World Health Organization 2016 new classifications; germ cell neoplasia *in situ* derived (GCNIS) and non-GCNIS derived (Figure 1) (4). GCNIS derived tumors usually present in the post-pubertal age and are more aggressive than non-GCNIS derived tumors which are usually seen in the pre-pubertal age (5).

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Traditionally, testicular tumors in children have been treated by radical high inguinal orchiectomy (1,6-8). As most pre-pubertal testicular tumors are benign (3,7-9), testis sparing procedures should be performed in selected cases especially with negative tumor markers (1,8). Here, we present the clinical and histological features and treatments of testicular tumors in pre-pubertal children in our center.

Materials and Methods

The clinical records of patients younger than 18 years treated for testicular tumors in our institution from January, 2006 to June, 2022 were reviewed retrospectively. Data were collected from the institutional electronic records. Their ages at diagnosis, clinical presentations, scrotal ultrasonographic findings, medical histories, tumor marker levels, surgical procedures, histopathological findings and outcomes were recorded.

Ethical approval was obtained from Zeynep Kamil Women and Children's Diseases Health Training and Research Hospital Clinical Research Ethics Committee (approval no: 202, date: 22.12.2021).

Results

A total of 12 patients were included in this study. All patients were younger than 3 years, except for one patient, who was 8 years old. The median age at primary diagnosis was 17 months (range: 1-107 months). The mean time from initial clinical presentation to diagnosis was 162 days (range: 3-840 days). The most common clinical presentation was testicular swelling (n=9, 75%). Three patients were diagnosed incidentally. Eleven out of the 12 patients had a palpable mass on preoperative physical examination. All patients who were later diagnosed with yolk sac tumor had a hard palpable mass, and one patient who was later diagnosed with epidermoid cyst had a hydrocele on preoperative physical examination. The left testis was affected in 8 (66.6%) cases and the right in 4 (33.4%) cases. None of the patients had a history of cryptorchidism.

Tumor marker profiles were available for nine out of the twelve cases. The tumor markers of the remaining 3 patients were taken, but the results could not be obtained from the records. Serum α-fetoprotein (AFP) was increased

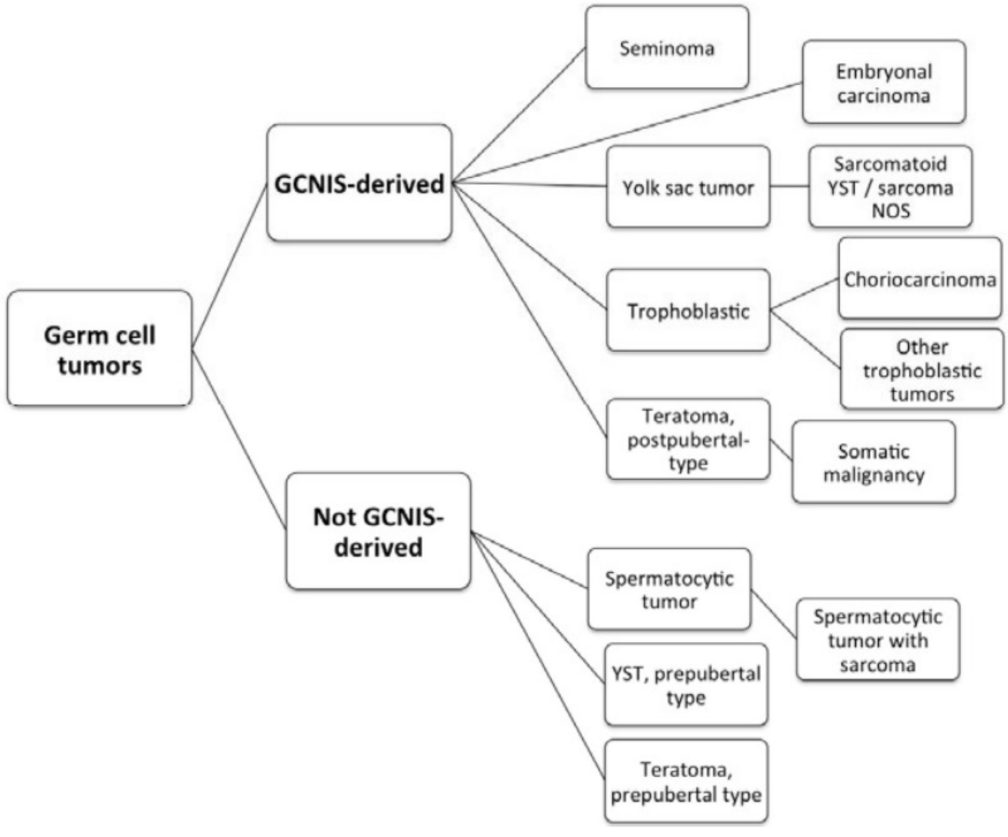

Figure 1. WHO-2016 new classification of germ cell neoplasia
WHO: World Health Organization, GCNIS: Germ cell neoplasia in situ derived

in 3 patients with yolk sac tumor (>1,000 ng/dL) and in one patient with mature cystic teratoma (1 month-old infant with an AFP concentration of 629 ng/dL). Preoperative β-human chorionic gonadotropin (β-hCG) levels were normal in all patients (<1.2 mIU/mL).

Of the 11 patients whose preoperative scrotal ultrasound could be obtained, 5 solid-cystic lesions, 3 cystic lesions, and 2 solid lesions were reported. Calcification was detected in 4 patients. Preoperative ultrasound findings were variable, but there was hyperechogenic cystic areas within the solid matrix or hyperechogenic cystic lesions in mature teratomas (n=4) and in epidermoid cysts (n=2), and hypervascularization in yolk sac tumors (n=3). There were no cases of bilateral or multiple tumors. CT of the chest, abdomen, and pelvis was performed before surgery in two patients who were later diagnosed with yolk sac tumor, and they were reported as normal. No metastatic spread due to primary testicular tumor was found.

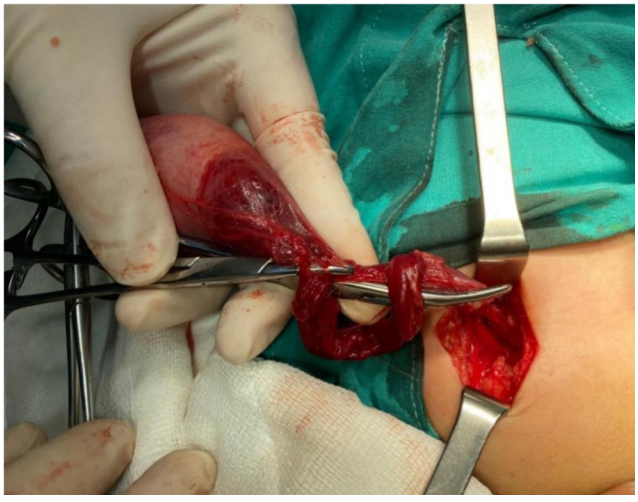

Figure 2. Patient with yolk sac tumor undergoing high inguinal radical orchiectomy

All surgical procedures were uncomplicated and the mean operation time of the patients for whom operation time records were available was 67.5 minutes (range 39-110 min). All 4 patients with malignant tumors and 3 patients with benign tumors underwent radical inguinal orchiectomy (Figure 2). Of the 5 tumors removed by testis preserving surgery, 2 were mature teratomas, 2 were epidermoid cyst and 1 was a benign multi-cystic lesion. They were treated by testicular-sparing surgery after frozen-section analysis (Figure 3).

Eight (66.6%) of the tumors were benign, and the most common subtype was mature cystic teratoma, and 4 (33.4%) of the tumors were malignant. Pathology revealed four (33.4%) yolk sac tumors, four (33.4%) teratomas, two (16.6%) epidermoid cysts, one (8.3%) hemangioma, and one (8.3%) benign multi-cystic lesion. The pathological characteristics and treatment outcomes are summarized in Table I.

There were no metastatic or local recurrences of the primary testicular tumor during a mean follow-up of 92

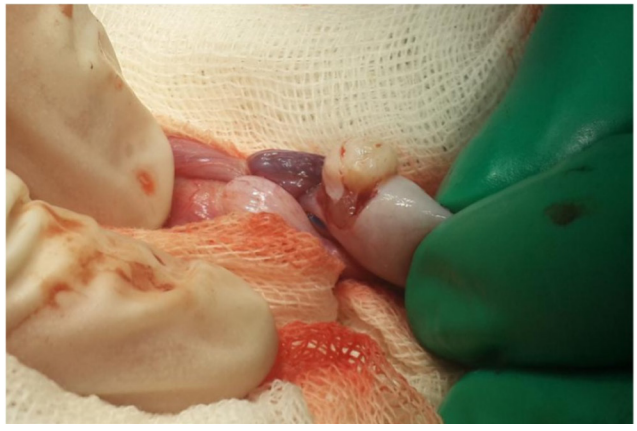

Figure 3. Patient with epidermoid cyst undergoing testis-sparing surgery

Table I. Summary of results

Histology	Number (%)	Median age at presentation (months)	Testis-sparing
	Non-GCNIS[a] derived		
Yolk sac	4 (33.4)	16	-
Mature cystic teratoma	4 (33.4)	13	2
Epidermoid cyst	2 (16.6)	71	2
	Others		
Hemangioma	1 (8.3)	34	-
Benign multi-cystic lesion	1 (8.3)	7	1
Total	12	25	6

[a]: Non-germ cell neoplasia *in situ*

months (2-198 months), except for one patient who died. Especially those patients with yolk sac tumor were referred to a multidisciplinary center with a pediatric oncology department in the early postoperative period. One of the four patients with yolk sac tumor died and no recurrence was observed in the remaining three patients with yolk sac tumor in a mean follow-up of 103 months (26-188 months).

Discussion

Testicular tumors are rare in children and they have a bimodal distribution. The first peak is at two years of age and comprises mainly non-GCNIS derived tumors (pre-pubertal teratoma and yolk sac lesions). Non-GCNIS derived germ cell tumors are the most common (77-85%) pre-pubertal testicular tumors and they are typically benign lesions (10,11). Patients with a prior history of undescended testis, a family history of testicular cancer or disorders of sexual development have been reported to have an increased incidence of testicular malignancy (12-14). Our patients had no history of undescended testis, family history of testicular cancer, or sexual development disorders. Similar to the literature, 83.4% of our patients were non-GCNIS-derived tumors.

The main symptom of pediatric testicular tumors is painless testicular mass. Hydrocele, hernia, bruising or precocious puberty are the less common findings (8). All patients in our series, except for those detected incidentally, presented with swelling in the testis.

Tumor markers are useful for the diagnosis and management of testicular tumors. Serum tumor markers include AFP, β-hCG and in some centers, lactic dehydrogenase. AFP (half-life 1-3 days) is secreted by the fetal yolk sac tissue and it is usually elevated in yolk sac tumors and some embryonal carcinomas (15). In infants, it is physiologically high and it returns to normal levels by the age of 1 year. Higher than age-related normal range of AFP suggests yolk sac tumor (90%) in pre-pubertal children with testicular tumors (16). β-hCG (half-life 5-7 days) is produced by syncytiotrophoblast tissues and it is elevated usually in choriocarcinoma or mixed tumor (15). In the present study, AFP was increased in 3 patients with yolk sac tumor (>1,000 ng/dL) and in one patient with mature cystic teratoma. β-hCG levels were normal in all patients (<1.2 mIU/mL).

The initial imaging method of a testicular mass is scrotal ultrasound. Ultrasound helps to predict tumor character. Ultrasonography has a sensitivity of almost 100% for the detection of testicular neoplasms (1). Ultrasound will help to distinguish intra-testicular and extra-testicular lesions and identify the lesion as benign or malign and also it rules out contralateral testicular masses (17). Unilocular lesions with anechoic content, well circumscribed with sharp borders, and avascularity are usually ultrasound features of benign masses (3,5). Epidermoid cysts tend to be more cystic in appearance and usually have echogenic debris. Characteristically mature teratomas appear as a hyper-echogenic cystic area in a solid matrix, and yolk sac tumors are usually solid lesions in appearance (3,6,8). In our series, 5 solid-cystic lesions, 3 cystic lesions, and 2 solid lesions were reported in preoperative scrotal ultrasound. According to our experience, while hyperechogenic cystic areas in the solid matrix were notable in benign lesions, hypervasularization was especially evident in malignant tumors. However, it should be noted that hypervascularization is not a specific sign of malignancy. CT or MRI imaging of the abdomen and pelvis are used for pre-operational staging and treatment planning for patients at high risk of metastasis (18).

Surgery plays an important role in the treatment of pediatric testicular tumors. In the past, the treatment of pre-pubertal testicular tumor was based on the treatment experience of adults. Inguinal radical orchiectomy has been the historical approach for all testicular tumors. In recent studies, most of the pre-pubertal testicular tumors were reported as benign, with a low propensity for local recurrence, and as metastasis is rare, testicular sparing surgery is preferred in appropriate cases (1,7,8,16,18). Liu et al. (19) reported 70 patients with mature teratoma and 33 epidermoid cyst, all of whom were treated with testis-sparing surgery. With a mean follow-up of 5 years, there were no cases of recurrence or testicular atrophy. Testis sparing surgery may be appropriate for all potentially benign tumors in pre-pubertal children with normal preoperative serum AFP and β-hCG levels, and salvageable normal testicular parenchyma on ultrasound (10,20). The long-term outcomes of testis-sparing surgery for benign testicular tumors are favorable and recent studies have reported its efficacy in preserving hormonal functions and fertility (21). At the same time, preserving the testis is important for its physiological and psychological effects on pre-pubertal patients (22). High radical orchiectomy is still recommended as the initial treatment for pre-pubertal testicular tumors, especially with high preoperative serum AFP values (3). The guidelines recommend high ligation at the level of the internal ring with an inguinal incision, and vascular control of the testis before mobilization by reaching a 5 cm proximal spermatic cord (23). In accordance

with these principles, testis-sparing surgery is performed in our institution with an inguinal incision. The inguinal canal is opened and after the spermatic cord is separated from the cremaster at the level of the internal ring, it is clamped at this level with a non-crush clamp. The testicle is taken out of the incision while protecting the wound. The mass capsule is excised without damage. Excision material is sent for frozen. If it is benign, the tunica is closed and the process is terminated. In pathology, pubertal changes in the tissue around the tumor should also be excluded because post pubertal tumors can be malignant (17). In this study, 66.6% were benign tumors and testis-sparing surgery was performed on 62.5% of them. Our approach to our patients has changed over time.

In a systemic review published in 2021 (5), including 269 patients who underwent testicular-sparing surgery, tumor recurrence was reported in one patient with mature teratoma. Six Leydig cell tumors had a positive surgical margin microscopically, and 2 of these cases underwent subsequent radical orchiectomy after parenteral choice due to their possible malignancy risk. No recurrence was reported in the other studies examined in this review. In our study, there was a patient with yolk sac tumor who died in the fifth month postoperatively while receiving chemotherapy. The remaining patients had no metastatic or local primary testicular tumor recurrence during a mean follow-up of 92 months (2-198 months).

Study Limitations

The limitations of the present study include its retrospective nature and its relatively small number of patients.

Conclusion

Testicular tumors in pre-pubertal children are uncommon. Most pre-pubertal tumors are benign and testicular sparing surgery can be performed on those patients with negative serum tumor markers. Inguinal radical orchiectomy is sufficient in the treatment of yolk sac tumor, which is the most common malignant tumor in this age group.

Ethics

Ethics Committee Approval: Ethical approval was obtained from Zeynep Kamil Women and Children's Diseases Health Training and Research Hospital Clinical Research Ethics Committee (approval no: 202, date: 22.12.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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Original Article

Spectrum of Congenital Lung Malformations in Children: Experience from A Tertiary Care Center

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ABSTRACT

Aim: A variety of developmental abnormalities of the tracheobronchial tree and pulmonary parenchyma are found in the newborn. There is limited data available on their presentation and clinical course from third world countries.

Materials and Methods: A retrospective review of the medical records of children with congenital lung malformations was conducted at our tertiary care hospital from June, 2014 to June, 2018.

Results: This study included 30 patients with 12 males and 18 females. The mean age at diagnosis was 13 months (range 1 month to 4 years). Congenital pulmonary airway malformation was the most common malformation present in 18 (60%) patients, followed by congenital lobar emphysema in 4 (13.3%), bronchogenic cyst in 3 (10%), bronchopulmonary sequestration in 2 (6.7%), bronchial atresia in 2 (6.7%) and pleuropulmonary blastoma in 1 (3.3%) patient. The most common presentation was recurrent upper respiratory tract infection (53.3%). Lobectomy was the most common surgical procedure performed in 86.6% of the patients, followed by excision of cyst in 10% of the patients. The post-operative complication rate was 30% with an overall survival rate of 93.3%. The average follow-up duration was 9 months.

Conclusion: The predominant lung malformation in this study was congenital pulmonary airway malformation. Recurrent respiratory tract infection with or without respiratory distress was the most common mode of presentation. Health education to raise awareness and emphasis on antenatal ultrasonography can avoid inordinate delays in diagnosis and treatment. Surgery is curative with good long-term outcomes.

Keywords: Congenital pulmonary airway malformation, bronchogenic cyst, pulmonary sequestration, congenital lobar emphysema

Introduction

Congenital lung malformations (CLMs) are a group of rare lung abnormalities affecting the airways, parenchyma, and vasculature. CLMs include congenital pulmonary airway malformations (CPAM), pulmonary sequestrations (PS), bronchogenic cysts, congenital lobar emphysema (CLE) and bronchial atresia (1). Many cases have overlapping features with CPAM like changes in an area of sequestered lung referred to as hybrid lesions (2,3). They are rare congenital malformations with a cumulative incidence of 30-42 cases per 100,000 individuals (4).

Due to the rarity of these malformations and the paucity of literature from the developing world, this study was conducted to share our experiences from a tertiary care center, which is the only center in the region catering to the treatment of such anomalies.

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Materials and Methods

This was a retrospective data review, conducted at a tertiary care hospital in northern India. The medical records of those patients diagnosed with CLM from June, 2014 to June, 2018 were evaluated. This study was undertaken after due approval by the Institutional Review Board of Sher-I-Kashmir Institute of Medical Sciences (approval no: 80/2018, date: 18.06.2018). The study population included children diagnosed as having CLM based on their clinical, radiological, and pathological features. We excluded syndromic children and those with major cardiac malformations. Data on their demographic profiles such as their age and gender, clinical presentation, baseline investigations, chest imaging studies (X-ray and computed tomography), hospital admissions, surgical interventions, surgical outcomes and follow-ups were retrieved. Any other relevant investigations such as bronchoscopy or dye study findings were also noted. Surgical details which included the timings of their surgical intervention, the type of surgery, the duration of the operation, intraoperative findings, and their intraoperative and postoperative complications were recorded. The CLMs studied included CPAM, CLE, bronchopulmonary sequestration, bronchial atresia, bronchogenic cysts and pleuropulmonary blastoma.

Statistical Analysis

The final data was entered into Microsoft Excel. Data analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA). The values of various parameters are presented as mean ± standard deviation, in absolute numbers or as percentages.

Results

Between June, 2014 and June, 2018, we studied 30 patients with CLMs in our hospital. The malformations were CPAM 18 (60%), CLE 4 (13.3%), bronchogenic cyst 3 (10%), sequestrations 2 (6.7%), bronchial atresia 2 (6.7%) and pleuropulmonary blastoma 1 (3.3%). The baseline characteristics of the patients are listed in Table I.

Most of the patients presented with respiratory tract infection/pneumonias (53.3%), followed by fever (26.6%), difficulty in breathing (23.3%) and pneumothorax (13%). Antenatal diagnosis was made on ultrasonography, which showed a cystic lesion in the chest in 3 (10%) patients. X-ray and computed tomography (CT) chest was performed in all patients (Figure 1). The most common finding on chest radiograph was cystic lucency in 83% of the patients, 50% of the patients had the presence of infiltrates, 33.3% patients had mediastinal shift to the opposite side, pneumothorax was identified in 13.3% of the patients and 6.6% of the patients had atelectasis. Chest ultrasound indicated a significant finding in 73.3% of the patients. Cystic lesion was the most common finding present in 36.6% of the patients, followed by consolidation in 33.3% of the patients, pleural effusion in 33.3%, pneumothorax in 13.3% and atelectasis was noted in 10% of the patients. CT of the thorax indicated abnormalities in lung parenchyma which included cystic lesions (73.3%), consolidation (33.3%), pleural effusion

Table I. Base line characteristics of the study population (n=30)

Characteristic	n (%) or mean
Age at presentation (months)*	13 (1.48)
Antenatal diagnosis	3 (10)
Male gender	12 (40)
Presenting symptom	
Asymptomatic	3 (10)
Symptomatic	27 (90)
Type of malformation	
Congenital pulmonary airway malformation	18 (60)
Congenital lobar emphysema	4 (13.3)
Pulmonary sequestration	2 (6.7)
Bronchogenic cyst	3 (10)
Bronchial atresia	2 (6.7)
Pleuropulmonary blastoma	1 (3.3)
Operation/Surgical resection done	30 (100)
Duration of follow-up (months)*	9 (3.36)
Associated malformations	8 (26.6)

*Mean and range

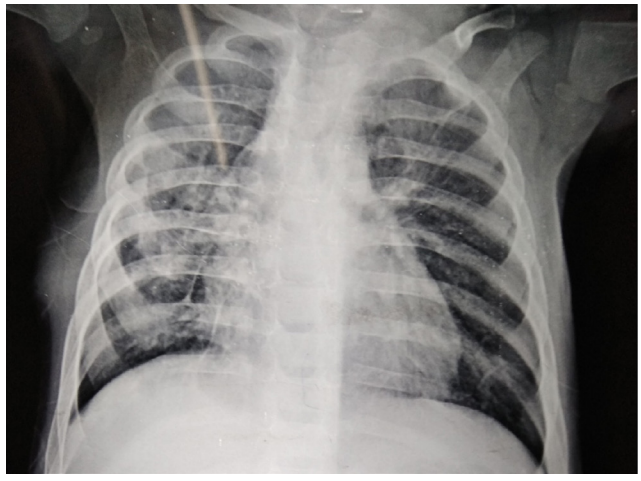

Figure 1. X-ray chest showing cystic lucency right upper lobe in a patient with right upper lobe congenital pulmonary airway malformation

(26.7%), pneumothorax (13.3%), bronchiectasis (10%) and atelectasis (10%) (Figure 2). The diagnoses of all of the patients was preoperatively established for CPAM, CLE, and bronchial atresia using different radiological investigations, particularly computed tomography, whereas the diagnoses of 50% of the patients with sequestration and a patient with pleuropulmonary blastoma were confirmed after histopathological examination.

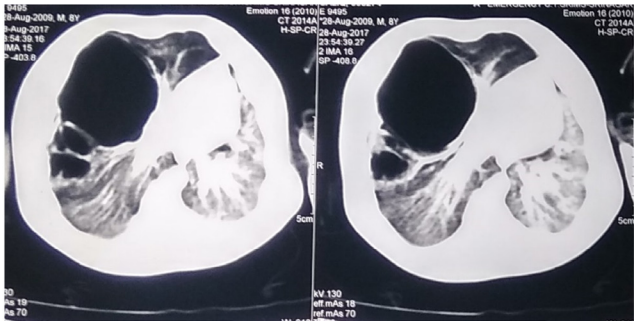

Figure 2. CT chest showing large cyst in right upper lobe congenital pulmonary airway malformation

Surgical procedures consisted of lobectomy (86.6%), cystectomy (10%), and others (3.3%) (Figure 3). Postoperative complications were pneumothorax (13.3%), sepsis (10%) and wound infection (6.6%). The clinical profiles, demography, and the outcomes of various CLMs are shown in Table II.

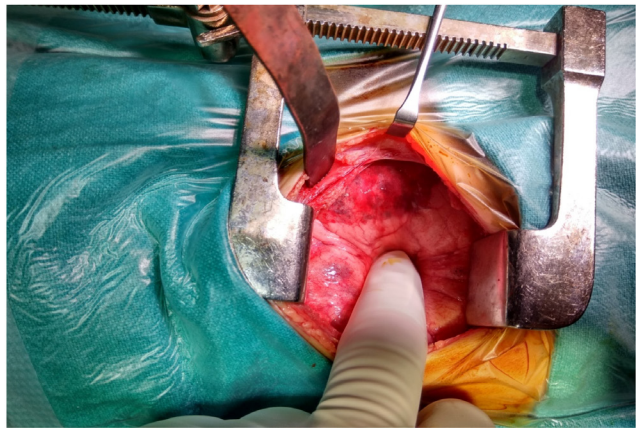

Figure 3. Intraoperative picture in a patient with right upper lobe congenital pulmonary airway malformation

Table II. Clinical profile, demographic characteristics, and outcome of various congenital lung malformations

Characteristic	CPAM (n=18)	CLE (n=4)	Sequestration (n=2)	Bronchogenic cyst (n=3)	Bronchial atresia (n=2)
Location, n (%)					
Right upper lobe	6 (33.3)	3 (75)	0	0	0
Right middle lobe	4 (22.2)	0	0	0	1 (50)
Right lower lobe	5 (27.7)	0	0	0	0
Left upper lobe	2 (11.1)	1 (25)	0	2 (66.6)	0
Left lower lobe	1 (5.5)	0	2 (100)	1 (33.3)	1 (50)
Age at diagnosis (mo)*	12.4 (2.48)	2.3 (2.3)	24	4.6 (1.9)	19 (14.24)
Age at surgery (mo)*	12.4 (2.48)	2.3 (2.3)	24	4.67 (1.9)	19 (14.24)
Male gender, n (%)	8 (44.4)	2 (50)	1 (50)	0	1 (50)
Presenting symptom, n (%)					
Fever	4 (22.2)	1 (25)	2 (100)	1 (33.3)	0
Recurrent chest infections	11 (61.1)	1 (25)	1 (50)	1 (33.3)	1 (50)
Fast breathing	4 (22.1)	2 (50)	0	0	0
Pneumothorax	4 (22.1)	0	0	0	0
Chest X-ray findings, n (%)					
Cystic lucencies	18 (100)	2 (50)	1 (50)	3 (100)	1 (50)
Mediastinal shift	7 (38.8)	2 (50)	0	1 (33.3)	0
Presence of infiltrates	10 (55.5)	1 (25)	1 (50)	2 (66.6)	1 (50)
Pneumothorax	4 (22.2)	0	0	0	0
Atelectasis	4 (22.2)	1 (25)	0	2 (66.6)	1 (50)
Postoperative complications, n (%)	5 (27.7)	1 (25)	1 (50)	0	1 (50)
Mortality, n (%)	0	1 (25)	0	0	0

*Mean and range, CPAM: Congenital pulmonary malformation, CLE: Congenital lobar emphysema

One operated case of pleuropulmonary blastoma died one year after surgery during follow-up by the medical oncology department. One case of Bronchogenic Cyst died 10 days after surgery (5 days after discharge from the hospital).

Discussion

Congenital pulmonary malformations are rare lesions which form during the embryological development phase of the lungs. The rates of diagnosis for these rare malformations in both the prenatal period and adulthood have increased because of advances in imaging methods (5).

In our study, CPAM was the most common type of CLM which is similar to previous reports (6-8). Bronchogenic cyst and CLE, however, have also been reported as major CPMs in some studies (9,10). We observed that the age distribution in our patients was 1 month to 4 years with a mean age of 13 months. The mean age at the time of diagnosis has been reported as being 13.1 months (11). CPAM and CLE in our study presented at an earlier age than PS. Patients with CPAM and CLE may present with symptoms earlier than patients with PS as the lesions of CPAM and CLE may compress the tracheobronchial tree, which can cause earlier symptom presentation (12).

On reviewing the clinical presentations of these lesions, respiratory tract infection/pneumonia (53.3%), fever (26.6%), difficulty in breathing (23.3%), and pneumothorax (13%) were the most commonly presenting symptoms. These findings are consistent with the reports of Jamero et al. (13). It has been observed that neonates and infants generally present with signs of respiratory distress (dyspnea, cyanosis) while older children mainly present with signs of pulmonary infection (fever, cough) (9,14).

Chest imaging is the cornerstone of diagnosis. Chest X-ray is usually the first line of investigation, and its findings vary with the type of malformation. CT is the gold-standard modality for the evaluation of anatomical structural defects and to define the anomalous blood supply (15). Large cystic lesions may present with changes affecting an entire hemi thorax, over inflation, mediastinal shift, and atelectasis (15). The location of the lung cyst in our study was in line with previously published reports (13). CPAM predominantly involved the right lung. The right upper lobe and the right lower lobe were more commonly involved. Bronchogenic cyst mostly involved the right lung. The right upper lobe was the most involved lobe. Congenital Lobar Emphysema involved the left lung in all cases. The left upper lobe was the most involved lobe, whereas PS involved the left lower lobe in all the cases.

All patients of CLM underwent some form of surgery in our study after preoperative optimization. While the decision making for children with symptomatic CLMs is reasonably straight forward, namely resection of the abnormality, there is ongoing debate regarding the need for and the timing of surgery in children with asymptomatic lesions. For those who support surgical intervention, the safety of pulmonary resection in infants and children is no longer a source of debate as its outcomes are generally good. Complication rates after surgery range between 6% and 9% and are mostly related to prolonged air leak (16). Mortality is a very rare occurrence in experienced hands and is thus not a significant outcome measure. The major surgical procedure in the present study was lobectomy and the main postoperative complications were pneumothorax, sepsis, and/or wound infection, similar to previous studies (8,17).

In the present study, there was an overall survival rate of 93.33%. There were 2 deaths. One operated case of pleuropulmonary blastoma died 1 year after surgery during follow-up by the medical oncology department. Pleuropulmonary blastoma can mimic CPAM. There should be a high index of suspicion in order to diagnose this rare and aggressive tumor (18). One case of bronchogenic cyst died 10 days after surgery (5 days after discharge from the hospital), probably due to aspiration.

Study Limitations

This study had several limitations. It was retrospective in design. The sample size was small due to the rarity of these malformations, which reduced the power of this study. Also, there was no data on lung function tests or long-term neurodevelopment outcomes. This study, nevertheless, gives an insight into these rare malformations.

Conclusion

In conclusion, CPAM was the most common CLM in our study. Recurrent respiratory tract infection with or without respiratory distress was the most common mode of presentation. Early detection of these relatively rare malformations will significantly improve the outcomes for such children. Surgery is the best modality of treatment with good outcome. Further studies from developing countries, with information regarding long-term follow-ups including lung function assessments, are needed.

Ethics

Ethics Committee Approval: The ethical approval was obtained from the Institutional Review Board of Sher-I-Kashmir Institute of Medical Sciences (approval no: 80/2018, date: 18.06.2018).

Informed Consent: Informed consent was obtained.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.N.M., W.J.S., A.S., N.A.B., A.A.B., R.H., S.K.A., Concept: S.M.A., G.N.M., W.J.S., A.S., N.A.B., A.A.B., R.H., S.K.A., Design: G.N.M., W.J.S., A.S., N.A.B., A.A.B., R.H., S.K.A., Data Collection or Processing: S.M.A., W.J.S., A.S., Analysis or Interpretation: S.M.A., G.N.M., W.J.S., A.S., N.A.B., A.A.B., R.H., S.K.A., Literature Search: S.M.A., W.J.S., A.S., Writing: S.M.A., W.J.S., A.S., S.K.A.

Conflict of Interest: The authors declared that there were no conflicts of interest.

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Original Article

Evaluation of Children with Nephrotic Syndrome: A Single Center Experience

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ABSTRACT

Aim: Nephrotic syndrome (NS) is the most common childhood glomerular disease manifested by proteinuria, edema and hypoalbuminemia. The aim of this study was to examine children with primary NS in terms of their clinical laboratory and histopathological features, and to evaluate their treatment responses.

Materials and Methods: Thirty-eight (21 boys/17 girls) patients followed up with primary NS were included in this study.

Results: The mean age at diagnosis was 6.4 years. The histopathological diagnoses were focal segmental glomerulosclerosis (FSGS) in 17 patients, minimal change disease (MCD) in 8, membranoproliferative glomerulonephritis (MPGN) in 3, and membranous glomerulonephritis in 1 patient. Those patients with MPGN were older than those with MCD and FSGS (p=0.035). Twenty-four patients were steroid sensitive. Steroid response rates were 88% in those patients with MCD, 41% in patients with FSGS and 33% in those with MPGN. At their last visit, three patients (7.9%) were diagnosed with chronic kidney disease.

Conclusion: NS is the most common glomerular disease of childhood. Early diagnosis and the histopathological features of this disease have an important place in its prognosis. Knowing the demographic, clinical and pathological features of the disease is helpful in monitoring its progress and its prognosis.

Keywords: Nephrotic syndrome, minimal change disease, focal segmental glomerulosclerosis

Introduction

Nephrotic syndrome (NS) is the most common childhood glomerular disease manifested by proteinuria, edema and hypoalbuminemia (1). The absence of concomitant diseases in patients diagnosed with NS is called primary NS. Idiopathic NS without signs of glomerular inflammation on kidney biopsy and primary glomerulonephritis, which is characterized by the presence of cells in the urinary sediment as well as signs of inflammation in biopsy, are classified as primary NS (2). The incidence of primary NS, which is one of the causes of chronic renal failure in childhood, has been reported as 1.5-2 per 100,000 individuals and its prevalence as 16 per 100,000 individuals per year (1,2). Due to hypercoagulability, infections, recurrent hospitalizations, the side effects of immunosuppressive treatments and the risk of progression to end-stage renal failure, NS is associated with high morbidity (3). The aim of this study was to examine those patients with primary NS in terms of their clinical laboratory and histopathological features, and to evaluate their treatment responses and also to contribute to the literature with our single center experience.

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Materials and Methods

Patients

The files of patients who were being followed up with a diagnosis of NS in Ege University Faculty of Medicine, Division of Pediatric Nephrology were retrospectively analyzed. Thirty-eight (21 boys/17 girls) patients with primary NS with a follow-up period of more than one year were included in this study. The patients were grouped according to their steroid responses and evaluated in terms of their admission and follow-up laboratory and clinical data and their histopathological diagnoses.

Definitions

NS: Protein excretion above 40 mg/m^2/h in collected urine or a protein/creatinine ratio above 2,000 mg/g in spot urine or >3+ protein in dipstick and concomitant hypoalbuminemia (<2.5 g/dL) and the presence of edema.

Remission: Protein less than 4 mg/m^2/h in collected urine or a protein/creatinine excretion rate below 200 mg/g in spot urine or <1+ protein on dipstick in the urine for 3 consecutive days.

Relapse: A protein/creatinine ratio above 2,000 mg/g in spot urine or >3+ protein on dipstick for 3 consecutive days.

Steroid sensitive NS: Complete remission after four weeks of steroid therapy.

Steroid resistant NS: Failure to achieve remission in the patient despite eight weeks of steroid therapy.

Steroid dependent NS: In patients who initially achieved remission with steroid therapy; two consecutive relapses during corticosteroid therapy or within 14 days after stopping treatment.

Frequent relapse NS: In those patients evaluated as steroid sensitive; two or more relapses within 6 months after their first response; or four or more relapses in any 12-month period (4).

Treatment and Follow-up

The patients were treated according to the Kidney Disease: Improving Global Outcomes clinical practice guidelines for glomerulonephritis and oral prednisolone was initiated as steroid therapy at the first step. In accordance with the protocol of our center, prednisolone was given as a single daily dose, at a dosage of 2 mg/kg per day [maximum (max): 60 mg]. After 4 weeks of treatment, the patient's response to steroid therapy was evaluated. In those patients with response (steroid sensitive NS), the treatment was switched to every other day (eod) and 2 mg/kg eod was continued for 2 months. Afterwards, the dosage was reduced by 0.5 mg/kg every 2 weeks and the total treatment was completed in 4.5 months. After one month of prednisolone treatment, those patients who could not achieve remission (steroid resistant NS) were treated with 3 days of pulse methylprednisolone (30 mg/kg per dose, max 1 gr) and the steroid was reduced to 2 mg/kg eod. These patients were re-evaluated at the 6th week of treatment.

In those patients who could not achieve remission, kidney biopsy was performed and immunosuppressive treatments other than steroids were started. As the first line therapy, prednisolone was used to achieve remission in those patients who were defined as steroid-dependent and frequent relapse. Later, immunosuppressive treatments other than steroids, called steroid sparing agents, were initiated. Renal biopsy was performed on those patients over 12 years of age at diagnosis with macroscopic hematuria lasting longer than 5 days, reduced Complement 3 (C3) levels, hypertension (HT), systemic disease and significant azotemia (2,4).

Statistical Analysis

All statistical analyses were performed using SPSS statistical software (v.22.0, IBM SPSS Statistics, IBM Corporation, Chicago, IL, USA). The Gauss distributions for continuous variables were evaluated using the Shapiro-Wilk test; they were expressed as mean ± standard deviation and median [minimum (min)-max]. Categorical variables were defined as numbers and percentages. Chi-squared analysis and Fisher's exact test were used for categorical variables, and the Mann-Whitney U test was used for continuous variables. Continuous variables under nonparametric conditions were compared using Student's t-test. The significance level used for these tests was $p<0.05$.

Ethical Consideration

This study was approved by the Ethics Committee of Ege University (approval date: 23.02.2023, approval no: 23-2.1T/48).

Results

Patients Characteristics and Histopathological Diagnoses

The mean age at diagnosis was 6.4±4.0 years, and the mean follow-up time was 5.6±4.1 years. While the male/female ratio was 1.2/1 in the entire NS population, this rate was 0.6/1 in minimal change disease (MCD),

0.5/1 in membranoproliferative glomerulonephritis (MPGN) and 3.5/1 in focal segmental glomerulosclerosis (FSGS) (p=0.044). Two of the patients had consanguinity between their parents, and four patients had a family history of NS. At the time of diagnosis, 5 (13.2%) of the patients had HT and 3 (7.9%) had macroscopic hematuria. Protein excretions in the collected urine were 152±146 mg/m^2/h; serum total protein was 4.2±0.63 mg/dL; serum albumin was 1.68±0.59 g/dL; serum total cholesterol was 363±181 mg/dL; urea was 28±22 mg/dL; and creatinine was 0.35±0.31 mg/dL. Kidney biopsy was performed on 29 (76.3%) of the patients. The median biopsy time was 12 months (min: 0.2 - max: 80 months).

The histopathological diagnoses were FSGS in 17 (58.6%) patients, MCD in 8 (21.1%), MPGN in 3 (7.9%), and 1 patient (2.6%) had membranous glomerulonephritis (MN). The pathological diagnoses of those patients presenting with macroscopic hematuria were MPGN (two patients) and FSGS (one patient). The histopathological diagnoses of the patients presenting with a diagnosis of HT were FSGS (two patients), MPGN (two patients) and MCD (one patient). The mean age at diagnosis was 6.3±3.5 years in MCD; 5.8±4.0 years in FSGS and 12.4±2.9 years in MPGN. The mean MPGN diagnosis age was significantly higher than the mean MCD and FSGS diagnosis ages (p=0.035) (Figure 1). The laboratory analyses of the patients at the time of their diagnoses are shown in Table 1; The urea, creatinine, uric acid and neutrophil levels in the diagnoses of those patients with MPGN were found to be statistically significantly higher than in those with MCD and FSGS (p=0.015; p=0.005; p=0.001; p=0.018). The mean high-density lipoprotein (HDL) and C3 levels of those patients with MPGN at diagnosis were statistically significantly lower than for those patients with MCD and FSGS (p=0.011; p=0.001). In all three groups, serum total protein, albumin, total cholesterol, triglyceride, low-density lipoprotein, HDL, sedimentation, C4 levels, white blood cell count and protein excretions in the collected urine were similar (p>0.05) (Table 1).

Treatment

The patients were classified according to their steroid responses; 24 (63%) patients were steroid sensitive, and 14 (37%) were steroid resistant NS. Ten (42%) of the patients diagnosed with steroid sensitive NS were steroid dependent and 1 (4%) had frequent relapses. Steroid response rates were 88% in those patients with MCD, 41% in those with FSGS and 33% in those with MPGN. Those patients with steroid sensitive NS were treated with steroid therapy during their recurrent attacks. Other immunosuppressive treatments used were calcineurin inhibitors (CNI) in 22 (88%) patients (19 cyclosporine, 3 tacrolimus), cyclophosphamide (CyA) in 12 (48%), mycophenolate mofetil (MMF) in 6 (24%), rituximab (RTX) in 4 (16%), and eculizumab in 1 (4%) patient.

In those patients with steroid-resistant NS, the response rates to other immunosuppressive treatments were, 57% to CNI, 33% to MMF, 33% to RTX, and 20% to CyA. The steroid-dependent patients' response rates were 100% to RTX, 70% to CNI, and 67% to CyA. The response rates to CNI, CyA, MMF and RTX treatments were similar between the steroid resistant and dependent NS patients (p>0.05). The non-steroid immunosuppressive treatments and their response rates are shown in Table 2.

Last Visit

At their last recorded visits, 33 (86.8%) of the patients were in remission, 2 (5.3%) were in partial remission, and 3

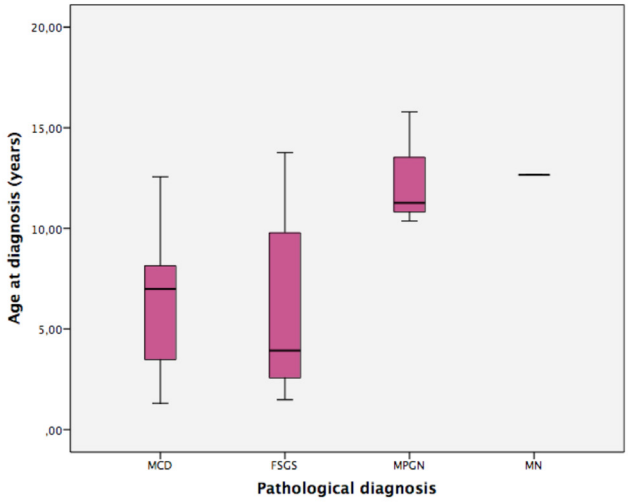

Figure 1. Age distribution of patients according to pathological diagnoses

(7.9%) were diagnosed as chronic kidney disease (CKD). The data of those patients followed up with CKD and those in partial remission are shown in Table 3.

The biochemical parameters of the patients such as urea, creatinine, uric acid values and neutrophil counts, which had been found to be significantly different among the groups according to their pathological diagnoses at the time of diagnosis, were similar in their last recorded visits (p>0.05). However, it was observed that HDL and C3 levels differed among the groups in their last recorded visits (Table 4).

Table I. Laboratory parameters at the time of diagnosis of patients according to pathological classification

	Minimal change disease		**Focal segmental glomerulosclerosis**		**Membranoproliferative glomerulonephritis**		
At the time of diagnosis	**Mean±SD**	**Median (Min.-Max.)**	**Mean±SD**	**Median (Min.-Max.)**	**Mean±SD**	**Median (Min.-Max.)**	**p-value**
Urea (mg/dL)	22±16	21 (4-45)	25±15	23 (16-62)	71±45	91 (31-120)	0.015*
Creatinine (mg/dL)	0.18±0.16	0.2 (0.1-0.4)	0.36±0.26	0.2 (0.1-1)	1.00±0.52	1.2 (0.6-1.6)	0.005*
Uric acid (mg/dL)	5.0±1.1	4.2 (3.9-6.5)	4.9±1.1	4.8 (3.0-7.6)	10.1±2.9	10 (8.0-12.2)	0.001*
Total protein (mg/dL)	4.0±0.6	4.1 (3.1-4-9)	4.2±0.6	4.5 (3.5-5.4)	4.3±0.7	4.7 (3.5-4.8)	0.868
Albumin (g/dL)	1.5±0.7	1.0 (0.6-2.4)	1.5±0.6	2.1 (0.6-2.5)	1.8±0.3	1.7 (1.6-2.2)	0.740
Total cholesterol (mg/dL)	452±177	514 (253-591)	380±211	312 (177-828)	229±180	196 (68-424)	0.517
Triglyceride (mg/dL)	168±107	170 (49-384)	198±139	102 (59-508)	245±136	249 (107-380)	0.804
LDL (mg/dL)	249±129	356 (75-402)	280±172	258 (61-651)	153±138	213 (33-304)	0.617
HDL (mg/dL)	49±13	51 (34-73)	65±17	62 (39-106)	27±15	34 (14-44)	0.011**
Sedimentation (mm/h)	59±32	60 (4-100)	57±43	58 (4-140)	37±29	28 (14-70)	0.863
WBC ($x10^3/mm^3$)	7.6±2.8	7.0 (4.4-13)	9.2±2.6	8.4 (6.0-15.4)	12.7±2.0	13.8 (10.3-14.1)	0.068
Neutrophil ($x10^3/mm^3$)	3.8±2.2	3.2 (1.5-8)	4.5±2.3	3.7 (1.3-9.5)	9.3±3.6	10.9 (5.3-12)	0.018*
Complement 3 (mg/dL)	107±13	112 (93-129)	137±20	127 (111-176)	45±27	45 (18-73)	0.001**
Complement 4 (mg/dL)	23±11	19 (12-36)	41±39	25 (12-61)	14±5	13 (8-19)	0.222
Urine protein ($mg/m^2/s$)	238±230	166 (63-642)	123±77	96 (41-291)	103±74	74 (56-182)	0.219

HDL: High-density lipoprotein, LDL: Low-density lipoprotein, SD: Standard deviation, Min.-Max.: Minimum-Maximum

Table II. Non-steroid immunosuppressive treatments and distribution of treatment responses

	All patients N=25		**Steroid resistant NS N=14**		**Steroid dependent NS N=10**		**Frequent relapse NS N=1**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
CNI treatment	22	88	13	93	9	90	0	0
CNI responsive	15	68	8	57	7	70	-	-
CyA treatment	12	48	5	36	6	60	1	100
CyA responsive	6	50	1	20	4	67	1	100
MMF treatment	6	24	3	21	3	30	0	0
MMF responsive	1	17	1	33	0	0	-	-
RTX treatment	4	16	3	21	1	10	0	0
RTX responsive	2	50	1	33	1	100	-	-
ECU treatment	1	4	1	7	0	0%	-	0
ECU responsive	1	100	1	100	-	-	-	-

CNI: Calcineurin inhibitor, CyA: Cyclophosphamide, MMF: mycophenolate mofetil, RTX: Rituximab, ECU: Eculizumab

Table III. Data of patients followed up with partial remission and chronic kidney disease

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Diagnose age (years)	4	11	9	10	10
Gender	Male	Male	Female	Male	Male
Creatinine level at diagnosis (mg/dL)	0.30	0.60	0.15	0.20	0.43
Histopathological classification	FSGS	FSGS	FSGS	FSGS	FSGS
Steroid response	Resistant	Resistant	Resistant	Resistant	Resistant
Genetic mutation	-	ADCK4	ADCK4	-	-
Follow-up (months)	35	43	142	42	13
Treatment	HD	PD	Coenzyme Q	Cyclosporine	Cyclosporine
Last visit	CKD Grade 5	CKD Grade 5	CKD Grade 4	Partial remission	Partial remission

FSGS: Focal segmental glomerulosclerosis, HD: Hemodialysis, PD: Peritoneal dialysis, CKD: Chronic kidney disease

Table IV. Laboratory parameters of the patients at last visit according to pathological classification

Last visit	Minimal change disease		Focal segmental glomerulosclerosis		Membranoproliferative glomerulonephritis		
	Mean±SD	Median (Min.-Max.)	Mean±SD	Median (Min.-Max.)	Mean±SD	Median (Min.-Max.)	p-value
Urea (mg/dL)	17±3	(13-22)	40±38	(15-137)	36±17	18-53	0.257
Creatinine (mg/dL)	0.53±0.10	(0.39-0.67)	1.37±2.2	(0.22-9.20)	0.77±0.21	(0.58-1.00)	0.532
Uric acid (mg/dL)	4.1±0.9	(2.6-5.7)	5.0±1.4	(3.1-8.3)	4.8±0.3	(4.5-5.1)	0.236
HDL (mg/dL)	52±15	(33-73)	70±45	(23-100)	122±94	(55-189)	0.019
Neutrophil (x10^3/mm^3)	3.7±1.1	(2.1-5.0)	4.4±2.1	(1.8-9.4)	3.6±1.9	(1.4-5.1)	0.643
Complement 3 (mg/dL)	94±8	(81-104)	133±27	(107-191)	92±11	(80-102)	0.002

HDL: High-density lipoprotein, SD: Standard deviation, Min.-Max.: Minimum-Maximum

Discussion

NS is the most common glomerular disease of childhood, and proteinuria, hypoalbuminemia and edema are its diagnostic criteria. Although the male/female gender ratio is variable, studies have reported male gender predominance at rates of 1.6-3.8 males to 1 female (1,4,5). In our study, although the male gender was more common, a much lower male predominance was found with a ratio of 1.2/1 compared to the literature. Looking at the gender distributions of NS subtypes, male dominance in minimal lesion disease (MLD) and FSGS has been reported in the literature at rates of 5-6/1, but this difference was found in our study only in the patient group diagnosed with FSGS (6).

Admission age has a prognostic importance on the histopathological diagnosis of this disease. The average age at diagnosis in idiopathic NS is 2-7 years; about 70% of patients with MCD are diagnosed under 5 years of age. The average age of FSGS at diagnosis is 6 years old (2,5,7). While MCD is the most common pathological diagnosis under 12 years of age, FSGS is common in the age group above 12 years of age (6). In our study group, the mean age of FSGS at diagnosis was found to be similar to MCD. We think that this difference in age and gender distribution is due to the fact that our study group consisted of a small patient population and our center is a reference center. MPGN, one of the primary glomerulonephritis group, is frequently diagnosed in late adolescence and adulthood (4). In our study, the mean age at diagnosis of MPGN was found to be 12.4 years, and this mean age was found to be significantly higher than the mean ages at diagnosis for MCD and FSGS.

HT suggest a diagnosis other than idiopathic NS (7). HT exists in one of every three patients in those individuals with MPGN, and the possibility of HT increases as the disease progresses (8). Macroscopic hematuria is a more common initial finding in patients with MPGN who were diagnosed in childhood compared to those diagnosed in their adulthood. The frequency of hematuria has been reported to be 20-30% in routine urine analysis in patients with MPGN (9). In our study, the prevalence of HT and macroscopic hematuria in patients with MPGN was 67%.

Histopathological features are of great importance in determining steroid sensitivity and the long-term prognosis in NS. Although indications for biopsy may differ between centers, the generally accepted indications are as follows; age of onset less than 1 year old or greater than 8 years old, steroid resistant NS unresponsive to 8-weeks prednisolone treatment, unusual clinical features such as HT and macroscopic hematuria and impairment in renal function. Depending on the patient population and the size of the centers, the biopsy and histopathological diagnosis frequencies vary in different studies, although FSGS and MLD are generally in the first two places (10-12). In this study, the frequency of biopsy was 76.3%, and similar to the literature, 17 (58.6%) of the patients were FSGS, 8 (21.1%) were MLD, 3 (7.9%) were MPGN and 1 (2.6%) was diagnosed with MN.

NS is also classified according to steroid sensitivity in addition to its histopathological classification, and this classification and the treatment responses of the patients also guide the prognosis. Steroid sensitivity rates were seen to vary between 80-90% in recent studies; and steroid dependence has been reported with a rate of up to 50% in steroid sensitive groups (13-15). In our patients, while the rate of steroid sensitive NS was 63%, 42% of these patients were steroid dependent.

In those patients with steroid-resistant NS, FSGS is the histopathological diagnosis with the highest rate of steroid resistance and the highest rate of CKD (16). The pathological diagnosis of 54% (8/14 patients) of the patients with steroid-resistant NS in our study was FSGS. The steroid response rate was 88% in those patients with MCD, 41% in those with FSGS; and 33% in those with MPGN. All of the patients who progressed to CKD were steroid-resistant NS and their histopathological diagnosis was FSGS. Table 3 shows the data of those patients followed up with partial remission and CKD.

Study Limitations

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

Conclusion

NS is the most common glomerular disease of childhood. Early diagnosis and the histopathological features of this disease have an important place in its prognosis. Knowing the demographic, clinical and pathological features of this disease is helpful in monitoring its progress and for its prognosis.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of Ege University (approval date: 23.02.2023, approval no: 23-2.1T/48).

Informed Consent: Written informed consent was obtained from all the patients or their parents/guardians.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Original Article

Optimal Skin Prick Test Panel for Detecting Respiratory Allergens in Children: A Retrospective Study

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ABSTRACT

Aim: The skin prick test (SPT) is the standard tool for determining respiratory allergen sensitizations. Different allergen sensitization patterns have been observed within countries and regions according to geographical and seasonal variations. This study aims to identify the sensitization pattern of children in different age groups and to define the minimum number and type of allergen extracts in an SPT to detect a sensitized child.

Materials and Methods: This retrospective study was conducted in the Outpatient Clinic of the Pediatric Allergy, Immunology, and Pulmonology Unit of a tertiary Children's Hospital from October 2019 to December 2020. Children aged between 2 and 18 years suspected of inhalant allergy with the presence of clinically relevant symptoms were included. The results of SPT were collected from medical records to determine the optimal panel to cover 95% of the sensitized children.

Results: A total of 1821 patients with SPT results were evaluated. Forty-three patients (2.4%) were excluded from the study because some allergen extracts did not apply. Consequently, 1778 children (male/female ratio of 1.33) were included in the study. The median age (interquartile range) was 8 years (2-18). The most common sensitizations were to grasses (Lolium perenne and Poa pratensis), trees (Olea europaea and Fraxinus excelsior), cereals (Avena sativa and Hordeum vulgare), animal dander (cat and dog), and weeds (Plantago lanceolata and Ambrosia artemisiifolia). The rate of sensitization tended to increase with age. Applying an SPT that included six allergen extracts for 2-5 years, five for 6-11 years, and four for 12-18 years was sufficient to identify 95% of sensitized children.

Conclusion: A test panel with six allergen extracts was sufficient to identify most of the sensitized children and adolescents suspected of allergy and had clinically relevant symptoms. An SPT with fewer allergen sources was required to detect older sensitized children than younger children.

Keywords: Aeroallergens, children, respiratory allergy, sensitization, skin prick test

Introduction

Atopic diseases have become increasingly prevalent in recent years and constitute a considerable proportion of pediatric outpatient visits (1). Aeroallergen sensitization is a significant factor in the development of these chronic illnesses and the increase in their prevalence. Although serum allergen-specific immunoglobulin E (IgE) can provide an indication when diagnosing IgE-mediated diseases, the skin prick test (SPT) has superior sensitivity and positive

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predictive value in comparison to specific IgE blood tests (1,2).

Some studies have revealed that aeroallergen sensitization changes with seasonal and geographical variations (3-6). However, most of these studies were concerned with the prevalence and distribution of airborne allergens and, thus, they did not reflect the patients' sensitization patterns. In the pan-European GA2LEN skin test study, 14 participating countries responded to this question, but this study's subjects consisted primarily of adults (7,8). In addition, some allergens are rarely observed in certain regions (2). Therefore, a limited number of allergen extracts may be used in children. Currently, no standardized test panel has been established across Europe. Determining the optimal number of allergen extracts to detect sensitized patients is more cost-effective and less painful for children. Therefore, it is advantageous from an economic and scientific view point.

This study aimed to investigate the aeroallergen sensitization patterns of children in different age groups and to determine the optimal number and type of SPT allergens needed to identify a child as being sensitized.

Materials and Methods

This retrospective study was carried out in the Outpatient Clinic of the Pediatric Allergy, Immunology, and Pulmonology Unit at a tertiary Children's Hospital in İzmir between October, 2019 and December, 2020. While the clinic serves as a referral center for the Aegean region of the country, patients may also be admitted on request; thus, it serves as both a primary and a tertiary health care center. Children aged 2 to 18 years with a suspected inhalant allergy and, in addition, a high likelihood of clinically relevant symptoms underwent SPTs. Patients were excluded if they had a negative histamine control or missing data. This study was approved by the Medical Research Ethics Committee of the Ege University Faculty of Medicine (approval no: 19-10.1T/34, date: 16.10.2019).

Aeroallergen Panel and SPT

An SPT is performed as a routine procedure in our clinic on the forearm of all children with clinical symptoms suggesting allergy. A standard panel consisted of 30 allergen extracts (Allergopharma, Germany), including house dust mites (Dermatophagoides pteronyssinus and Dermatophagoides farinae), animal dander (cat, dog, and horse), Blattella germanica, grass pollens (Dactylis glomerata, Phleum pratense, Lolium perenne, Poa pratensis, and Festuca pratensis), weed pollens (Artemisia vulgaris, Urtica diocia, Parietaria officinalis, Plantago lanceolata, and Ambrosia artemisiifolia), tree pollens (Alnus glutinosa, Ulmus scabra, Populus alba, Olea europaea, Fraxinus excelsior, Tilia cordata, and Acer pseudoplatanus), cereal pollens (Hordeum vulgare, Avena sativa, and Secale cereale), and molds (Alternaria alternata, Aspergillus fumigatus, Cladosporium herbarum, and Penicillium notatum), histamine as a positive control (10 mg/mL of histamine phosphate), and 0.9% sterile saline as a negative control. The selection of aeroallergens was based on their availability. The SPTs in our study were evaluated 15-20 minutes after their application. A positive result was defined as a wheal diameter ≥3 mm compared to the negative control. The presence of sensitization for a patient was determined as a positive SPT result for at least one of the allergen extracts tested in our study.

Statistical Analysis

Quantitative data were reported as mean ± standard deviation or median with an interquartile range. The prevalence of sensitization to each allergen extract was determined using frequencies and percentages. A step-by-step conditional approach was used to classify allergens from the one which caused the highest increase in the prevalence of sensitization to the one which gave the lowest increase. First, the most prevalent allergen was determined. Then, the highest prevalence of sensitization was investigated in the subgroup of subjects not sensitized to the previous allergen in order to detect the following allergen with the highest increase in the prevalence of sensitization (8). This procedure was repeated for the whole study group until the number and type of allergens needed were determined in order to identify at least 95% of sensitized subjects. Furthermore, the same process was repeated with the patients allocated by their age subgroups: 2-5 years, 6-11 years, and 12-18 years. Statistical analysis was performed using IBM SPSS V.20.0 (SPSS, Chicago, IL).

Results

A total of 1,821 patients with SPT results were evaluated. Forty-three patients (2.4%) were excluded because some allergen extracts had not been applied. Finally, 1,778 children (male/female ratio of 1.33) with a median age of 8 years (5.0-12.0) were included in this study. The sensitization rate was higher in those children aged 12-18 years than in those aged 2-5 or 6-11 years (77.0% vs. 38.6% and 60.8%, respectively). Multiple sensitizations to aeroallergen extracts were found in 815 (45.8%)

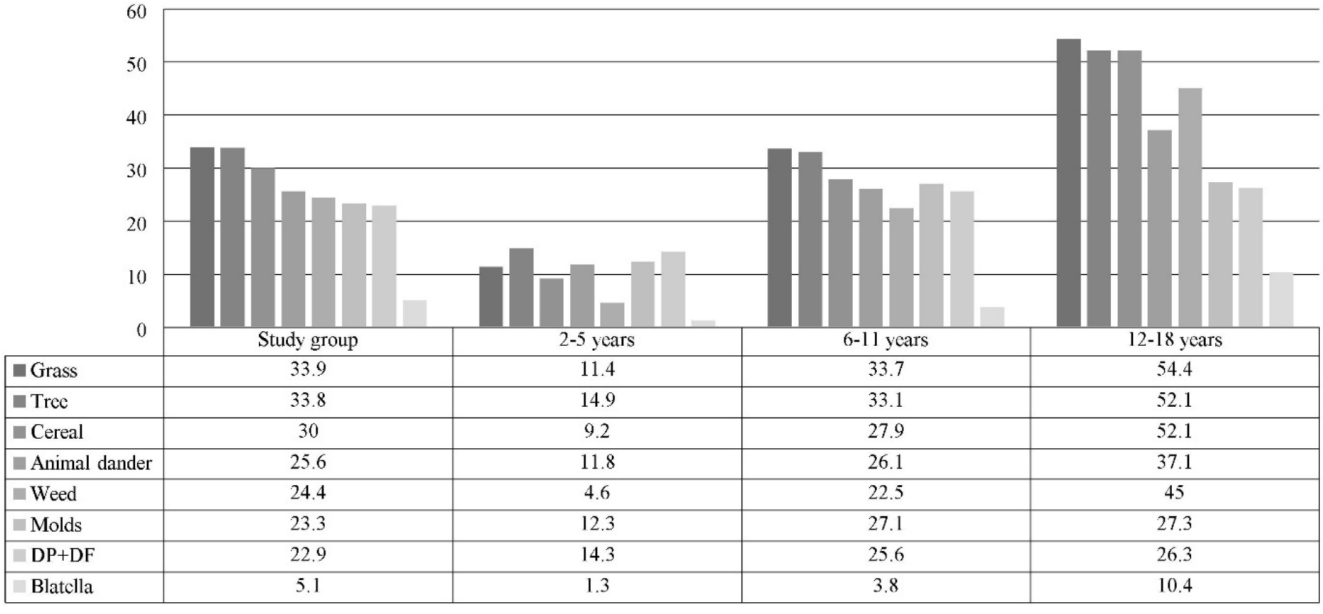
children and this tended to increase with age (Table I). The distribution of aeroallergen sources among the sensitized children is presented in Figure 1.

The most common allergens were Lolium (32.6%), Poa (32.0%), Phleum (31.8%), Dactylis (31.3%), and Olea (31.3%; Table II). Applying five allergen extracts (Lolium, D. pteronyssinus, cat, Alternaria, and Olea) was sufficient to detect 95% of all sensitized patients. Furthermore, we showed that testing with six allergen extracts for children aged 2 to 5 years (D. pteronyssinus, Olea, cat, Alternaria, Poa, and D. farinae) and five for those aged 6 to 11 years (Lolium, D. pteronyssinus, cat, olea, and Alternaria) identified 95% of SPT sensitization. Finally, four allergen extracts (Lolium, D. pteronyssinus, cat, and Alternaria) were required to detect 95% of sensitized children between 12 and 18 years of age (Table III).

Table I. Characteristics of the study population

	All patients n=1778	**2-5 years n=456**	**6-11 years n=813**	**12-18 years n=509**
Age, year				
Mean ± SD	8.9±4.1	4.1±0.9	8.2±1.7	14.4±1.9
Median (IQR)	8.0 (5.0-12.0)	4.0 (4.0-5.0)	8.0 (7.0-10.0)	14.0 (13.0-16.0)
Gender, n (%)				
Male	1016 (57.1)	258 (56.6)	478 (58.8)	280 (55.0)
Female	762 (42.9)	198 (43.4)	335 (41.2)	229 (45.0)
SPT, n (%)				
Positive	1062 (59.7)	176 (38.6)	494 (60.8)	392 (77.0)
Mono-sensitization	247 (13.9)	84 (18.4)	119 (14.6)	44 (8.6)
2 allergens	179 (10.1)	41 (9.0)	82 (10.2)	56 (11.0)
≥3 allergens	636 (35.7)	51 (11.2)	293 (36.0)	292 (57.4)

SD: Standard deviation, IQR: Interquartile range, SPT: Skin prick test



	Study group	2-5 years	6-11 years	12-18 years
Grass	33.9	11.4	33.7	54.4
Tree	33.8	14.9	33.1	52.1
Cereal	30	9.2	27.9	52.1
Animal dander	25.6	11.8	26.1	37.1
Weed	24.4	4.6	22.5	45
Molds	23.3	12.3	27.1	27.3
DP+DF	22.9	14.3	25.6	26.3
Blatella	5.1	1.3	3.8	10.4

Figure 1. Distribution of aeroallergen extracts among sensitized children for the whole study group and age subgroups
DP: Dermatophagoides pteronyssinus, DF: Dermatophagoides farinae

Table II. Distribution of the frequencies of sensitization for each allergen used in the skin prick tests in the whole study population and by age subgroups

	Study population n=1,778 n (%)	**2-5 years n=456 n (%)**	**6-11 years n=813 n (%)**	**12-18 years n=519 n (%)**
House dust mites				
D. pteronyssinus	385 (21.7)	61 (13.4)	195 (24.0)	129 (25.3)
D. farinae	372 (20.9)	57 (12.5)	191 (23.5)	124 (24.4)
Animal danders				
Cat	434 (24.4)	54 (11.8)	200 (24.6)	180 (35.4)
Dog	226 (12.7)	21 (4.6)	92 (11.3)	113 (22.2)
Horse	36 (2.0)	4 (0.9)	16 (2.0)	16 (3.1)
Blatella germanica	90 (5.1)	6 (1.3)	31 (3.8)	53 (10.4)
Grass pollens				
Lolium perenne	579 (32.6)	48 (10.5)	258 (31.7)	273 (53.6)
Poa pratensis	569 (32.0)	49 (10.7)	252 (31.0)	268 (52.7)
Phleum pratense	565 (31.8)	47 (10.3)	247 (30.4)	271 (53.2)
Dactylis glomerata	556 (31.3)	46 (10.1)	241 (29.6)	269 (52.8)
Festuca pratensis	549 (30.9)	46 (10.1)	243 (29.9)	260 (51.1)
Weed pollens				
Plantago lanceolata	341 (19.2)	14 (3.1)	141 (17.3)	186 (36.5)
Ambrosia artemisiifolia	196 (11.0)	8 (1.8)	83 (10.2)	105 (20.6)
Artemisia vulgaris	184 (10.3)	6 (1.3)	75 (9.2)	103 (20.2)
Parietaria officinalis	115 (6.5)	1 (0.2)	45 (5.5)	69 (13.6)
Urtica diocia	85 (4.8)	0 (0)	29 (3.6)	56 (11.0)
Tree pollens				
Olea europaea	557 (31.3)	59 (12.9)	243 (29.9)	255 (50.1)
Fraxinus excelsior	466 (26.2)	50 (11.0)	200 (24.6)	216 (42.4)
Alnus glutinosa	161 (9.1)	9 (2.0)	73 (9.0)	79 (15.5)
Tilia cordata	158 (8.9)	5 (1.1)	61 (7.5)	92 (18.1)
Ulmus scabra	149 (8.4)	6 (1.3)	67 (8.2)	76 (14.9)
Populus alba	133 (7.5)	4 (0.9)	60 (7.4)	69 (13.6)
Cereal pollens				
Avena sativa	508 (28.6)	37 (8.1)	213 (26.2)	258 (50.7)
Hordeum vulgare	496 (27.9)	34 (7.5)	210 (25.8)	252 (49.5)
Secale cereale	465 (26.2)	30 (6.6)	195 (24.0)	240 (47.2)
Molds				
Alternaria alternata	359 (20.2)	52 (11.4)	194 (23.9)	113 (22.2)
Cladosporium herbarum	131 (7.4)	12 (2.6)	61 (7.5)	58 (11.4)
Aspergillus fumigatus	89 (5.0)	7 (1.5)	42 (5.2)	40 (7.9)
Penicillium notatum	48 (2.7)	4 (0.9)	20 (2.5)	24 (4.7)

Table III. The suggested test panel for different age groups and the percentage of sensitization by certain aeroallergen extracts

	n	%	Cumulative %
2-5 years			
D. pteronyssinus	61	34.7	34.7
Olea europaea	51	29.0	63.7
Cat	24	13.6	77.3
Alternaria alternata	18	10.2	87.5
Poa pratensis	12	6.8	94.3
D. farinae	3	1.7	96.0
Others	7	4.0	100
6-11 years			
Lolium perenne	258	52.2	52.2
D. pteronyssinus	119	24.1	76.3
Cat	52	10.5	86.8
Olea europaea	27	5.5	92.3
Alternaria alternata	18	3.6	95.9
Others	20	4.1	100
12-18 years			
Lolium perenne	273	69.6	69.6
D. pteronyssinus	65	16.6	86.2
Cat	26	6.6	92.8
Alternaria alternata	13	3.3	96.1
Olea europaea	6	1.5	97.6
Others	9	2.4	100
Whole study group			
Lolium perenne	579	54.5	54.5
D. pteronyssinus	235	22.1	76.6
Cat	109	10.3	86.9
Alternaria alternata	61	5.7	92.6
Olea europaea	38	3.6	96.2
Blatella germanica	9	0.8	97.0
Aspergillus fumigatus	7	0.7	97.7
D. farinae	5	0.5	98.2
Phleum pratense	3	0.3	98.5
Others	16	1.5	100

Discussion

This study determined that grass pollens were the most common allergen source in children, followed by tree and cereals pollens. While sensitization to tree pollens and house dust mites was more common in those children aged 2-5 years, we found that sensitization to grass and tree pollens was more frequent in those aged 6-11 and 12-18 years. Furthermore, the application of an SPT involving a limited number of allergen extracts (4-6) was sufficient to identify 95% of the sensitized children.

Geographical and climate variations play a crucial role in sensitization patterns. These relationships were revealed in several extensive studies, such as the European Community Respiratory Health Survey and the International Study of Asthma and Allergies in Childhood (5,6). Turkey has wide geographical diversity, containing Mediterranean, Black Sea, and Turanian climate regions. The climatic condition of this study setting is classified as Csa (warm temperature, fully humid, hot summer) according to the Köppen-Geiger climate map (9). Earlier studies under the same climatic conditions demonstrated that grass pollens were the most common sources of aeroallergens, followed by weed and tree pollens (10,11). Our results were similar to those of most European countries, including Denmark, the UK, Greece, Poland, and the Netherlands, where sensitization to grass pollens varied between 19.5 and 69.9%. However, we noted that house dust mites were the leading allergen in some countries, including Portugal, France, Italy, and Belgium (7).

Studies on determining the optimal and most cost-effective SPT panel began with the population-based European Community Respiratory Health Survey. The authors showed that seven allergen extracts (D. pteronyssinus, cat, grass, birch, olive, Alternaria, and Cladosporium) were adequate for epidemiological studies in Europe (6,12). Subsequently, the GA2LEN study group conducted patient-based research and found that a similar test panel of eight allergen extracts was sufficient to detect more than 95% of sensitized patients. However, they highlighted that there may be some differences in the number of allergen extracts between countries (e.g., two allergen extracts in Switzerland and nine allergen extracts in France) (8). We propose a test battery which includes five allergen extracts (Lolium, D. pteronyssinus, cat, Alternaria, and Olea) as being sufficient to identify 95% of sensitized children in our study population. Our results agreed with those of most European countries. Surprisingly, in another study involving 2,457 children conducted in the center of Turkey, the authors showed that a test panel of 12 allergen extracts identified more than 95% of the patients (2). As mentioned earlier, this discrepancy could be attributed to the different climate conditions and geographical location. While our study was conducted in the coastal part of the country, the other study was conducted in central

Anatolia, defined as Dsb (Mediterranean-influenced warm-summer humid continental climate) according to the Köppen-Geiger climate map. Another explanation might be associated with the fact that their patient population came from distinct geographical locations, such as from the East, North, and South of Turkey, resulting in increased heterogeneity in allergen sources. A birth cohort of preschool-age children determined that four allergen extracts were sufficient to identify 94% of sensitized subjects (13). Şahiner et al. (2) determined that the minimum number of allergens in an SPT was 12, 8, and 7 for preschool, school, and adolescence patients, respectively. Sensitization to aeroallergens is related to environmental exposures, and it is also inevitable to encounter specific allergens as a child grows older. Consequently, the spectrum of allergen sources is more uniform in older children than in younger ones, as shown by the increase in the rate of all allergen sources with age in our study. This predomination decreases the number of allergen extracts necessary to reach a total sensitization rate of 95%.

Our results showed that the sensitization to cereal and weed pollens was 30% and 24.4%, respectively. Reports from our country showed that cereal sensitization ranged between 32.1% and 45% (2,10,11), while weed sensitization ranged between 7% and 23% (10,14). When we consider Ambrosia sensitization, which was tested in both the GA2LEN study and our study, it was 11% in this study. On the other hand, the sensitization to Ambrosia in Greece and Portugal, where the Mediterranean climate is dominant, as is the case Izmir, ranged between 11.7% and 12.4%, and it reached 53.8% in Hungary (7). Most European countries are characterized as climate regions of Cfb (warm temperature, fully humid and warm summer) and Dfb (snow, fully humid and warm summer) according to the Köppen-Geiger climate map (9). Therefore, the sensitization to weed and grass pollens is higher in those countries in comparison to Turkey. Olea europaea was another major allergen in our study and it was identified in 31.3% of sensitized children. Our result was supported by previous studies conducted in the Aegean region, which determined the Olea sensitization rate to be between 24% and 30% (10,15). Higher Olea sensitization may be associated with the fact that Olea plantations are more common in Izmir, which is located on the west coast of the country, in comparison to the center of the country.

In this study, sensitization to house dust mites (D. pteronyssinus or D. farinae) was found to be 22.9%. This result was consistent with previous studies in our country (2,10,14,16). According to the GA2LEN skin test study, sensitization to house dust mites was rare in Central and Western Europe (7). In contrast, it was notably higher in Nordic and Mediterranean countries (32.7% in Greece and 68.8% in Portugal for D. pteronyssinus) (7). Although cat ownership is low in our country (17), cat sensitization was determined to be 24.4% in the present study. As pet ownership is more common in Europe, the sensitization rates there were higher than our results (49.3% in Denmark and 42.1% in Switzerland) (7). Many cat-allergic patients became sensitized by environmental exposure to cats (18,19). Alternaria and Cladosporium were the most prevalent molds, with 20.2% and 7.4%, respectively. From a population-based study in the United States, Alternaria sensitization was reported to be 36% (20). In Europe, sensitization rates were low in many countries, but high levels were observed in Hungary and Finland (18.6% for Alternaria and 7.1% for Cladosporium), as in our study (7). An implication of these findings may suggest having a particular test battery for each clinic related to the region. In addition, further studies focusing on the relationship between aeroallergen sensitization and their clinical relevance need to be considered.

Study Limitations

This study had some limitations. Firstly, this was a patient-based study focusing on children with clinical allergy symptoms, so the results may not be in line with those of epidemiological studies. Secondly, this study investigated only sensitization patterns and did not determine the relationship between the allergen and its clinical relevance. As it was a single-center study, some allergen sources may have been omitted, resulting in a decrease in the generalizability of the findings of this study. Nevertheless, the center admits patients from all parts of the Aegean region.

Conclusion

Identifying the sensitization patterns of children in different age groups can help select the allergen extracts to be used in SPT panels, thus preventing the use of those allergen extracts which are unnecessary. Regarding those cities with a Mediterranean climate, a standardized 6-allergen extract panel might be sufficient to determine 95% of sensitized children.

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Ethics

Ethics Committee Approval: This study was approved by the Medical Research Ethics Committee of the Ege University Faculty of Medicine (approval no: 19-10.1T/34, date: 16.10.2019).

Informed Consent: This was a retrospective study.

Authorship Contributions

Concept: A.E., G.K.Ö., F.G., E.D., Design: A.E., G.K.Ö., F.G., E.D., Data Collection and/or Processing: A.E., G.K.Ö., F.G., E.D., Analysis or Interpretation: A.E., G.K.Ö., F.G., E.D., Literature Review: A.E., G.K.Ö., F.G., E.D., Editing of the Manuscript: A.E., G.K.Ö., F.G., E.D., Writing: A.E., G.K.Ö., F.G., E.D.

Conflict of Interest: The authors declared that there were no conflicts of interest.

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Original Article

The Impact of a Humanoid Robot on Children's Dental Anxiety, Behavior and Salivary Amylase Levels: A Randomized Clinical Trial

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ABSTRACT

Aim: With the spread of technological possibilities, the idea that humanoid robots can accompany medical interventions has gained momentum. The objectives of this two-armed randomized controlled study were (i) to assess the effects of a human-like robot on behavior guidance during children's dental treatment, by a comparison of the dental anxiety scale, behavioral scale, pulse rate and amylase levels in the saliva and (ii) to determine whether the children would like to have treatment with a humanoid robot.

Materials and Methods: One hundred two children (52 girls, 50 boys; mean age: 6.71±1.43 years) were included. The exclusion criteria were children showing definitely negative behavior (Frankl 1) during dental prophylaxis at the first visit and those children who had had dental treatment previously. Fifty children were assigned to the robot group (RG) and 52 children were assigned to the control group (CG). The Facial Image scale (FIS), Frankl Behaviour Rating scale (FBRS), physiological pulse rate and salivary alpha amylase (sAA) levels were used to assess the stress related changes. The Mann-Whitney U test and the Student's t-test were used to compare the groups. In-group comparisons were tested with the Wilcoxon signed-rank test. The chi-squared test, Continuity (Yates) correction, and the Fisher-Freeman-Halton test were used to compare qualitative data. Statistical tests were considered significant at a p-value set at 0.05.

Results: The post-treatment FIS scores of the RG in the 6-10-year-olds were significantly lower than in the CG ($p<0.05$). Post-treatment FBRS scores were statistically significantly higher in the RG than in the CG in both younger and older children ($p<0.05$). In children aged between 6 and 10 years, pulse rates during and after treatment in the RG were significantly lower than those in the CG ($p<0.05$). No correlation was found between the children's anxiety/behavior and their sAA levels.

Conclusion: The robot was found to be effective in reducing dental anxiety and pulse rates in children aged 6-10 years, and it was preferred more by the children of this age.

Keywords: Dental anxiety, human computer interaction, robotic, salivary amylase

Introduction

Despite modern technological advances, dental procedures still cause anxiety and fear reactions. Dental anxiety is a very common condition in children who receive dental treatment and it can cause problems for the dentist and the patient alike (1). Although dental anxiety can be seen at any age, it usually occurs in childhood. The dental anxiety problem seen in childhood may continue

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into adulthood, causing people to avoid dental treatment and consequently negatively affect their oral and dental health (2).

Various psychological and pharmacological techniques are used to insulate pediatric patients from dental anxiety during their dental treatment. Behavior guidance techniques are based on understanding the social, emotional and cognitive development of children in order to provide effective treatment and establish social behavioral guidance. Non-verbal communication, distraction, positive encouragement, voice control, and tell-show-do are among the non-pharmacological behavioral guidance techniques (3).

We are in an era of the increasing development and testing of social robots in the medical field (4). There are over a dozen existing applications with healthcare robots including changing dressings, blood tests, catheter insertion/removal, oxygen tube insertion, IV start/removal, vaccinations, and electroencephalogram (5,6). There are robots with different applications which attract the attention of children, train them and support them with cognitive-behavioral interventions e.g. managing illnesses by promoting the correct behavior in those children with chronic health conditions, helping to distract children undergoing acute medical procedures or during vaccinations or comforting them as a friend (7).

There is an increasing focus on children's interactions with robots. Socially assistive robots have the ability to assist to ease the procedures in order to reduce children's anxiety and distress during their hospital visits (8-10). NAO is a programmable, autonomous humanoid robot. The NAO has been used to develop adaptive behaviors in children in a number of studies (11-14). However, there was no study to-date about the use of social robots in dentistry for reducing dental fear and anxiety.

Saliva can be analyzed for biomarkers as it reflects many systemic and local biochemical and physiological processes. The non-invasive and easy nature of saliva sampling make it a very useful and relatively stress-free diagnostic alternative to blood sampling in neuroscience and psychology. Therefore, it is of value in studying anxiety towards a dental procedure. Saliva secretion is regulated by the autonomic nervous system (ANS). sAA has been suggested as an index of autonomic activity as a result of its release from the salivary glands being under the strong control of the local sympathetic nerves and so its salivary concentration rapidly increases in certain circumstances (15,16). As an ANS marker, sAA is a valid indicator for acute sympathetic nervous system stress response (16). sAA is more sensitive to subtle psychological stress compared to systolic blood pressure or pulse rates (17).

The primary objective of this study was to assess the effects of a human-like robot on the behavior guidance during children's dental treatment, by comparisons of the dental anxiety scale, the behavioral scale, pulse rates and amylase levels in the saliva. Our secondary objective was to determine whether the children in the RG would like to have future treatment with the NAO.

Materials and Methods

This randomized controlled clinical trial was approved by the İstanbul University Faculty of Dentistry Clinical Research Ethics Committee (2014/461) and it was conducted within ethical standards in accordance with the Declaration of Helsinki. Informed consent was obtained from all of the children and their parents. This study was carried out according to the CONSORT 2010 statement (18). The study protocol was registered on ClinicalTrials (NCT05238246).

The following focused question was developed in accordance with the recognized Patient, Intervention, Comparison, and Outcome (PICO) method: In children who were between 4 and 10 years old, during their first experience with the dentist and in need of restoration or a pulpotomy (P); what was the effect of techno-psychological distraction (I) as compared to the conventional behavior management method (C)? Was there any decrease in dental anxiety observed by physiological or psychological measurements (O)?

Selection and Description of Participants

Healthy children aged between 4 and 10 years, having their first dental visit and requiring a pulpotomy for a primary molar were selected. We included only children aged 4 years and older in our study, as younger infants have low cooperation skills. Those children who agreed to complete the questionnaires and who gave informed consent and were accompanied by at least one parent participated in this study. Children who had a history of systemic diseases or who were medically compromised were not included in this study.

Inclusion criteria were (a) healthy children who did not have any genetic syndrome or systemic diseases in their medical history, who were not physically or mentally disabled, (b) those who had had no previous dental experience, (c) and who needed pulpotomy in at least one mandibular primary molar.

Those children with a significant systemic disease in their medical history or with disabilities, and those who had previously been taken to the dentist for treatment, and those who were unaccompanied or who refused to fill out the questionnaire, those children who exhibited definitely negative behavior (Frankl 1) during their dental prophylaxis at the first visit and those children who had had dental treatment before were not included in this study.

The G*Power program was used to determine the number of participants, the effect size for the facial image scale (FIS) score (19) was d (effect size): 0.637, SD: 1.25, Power: 0.80 and α: 0.05, and the minimum number of participants for each group was calculated to be n=22.

Sample Characteristics

One hundred and two children who met the inclusion criteria took part in this research. Fifty children were enrolled in the robot group (RG) and fifty-two children were enrolled in the control group (CG). The mean age of all of the children was 6.71±1.43 years (Table I). The CONSORT flow chart for participant enrollment is shown in Figure 1.

Randomization

Participants were randomized in a 1:1 ratio for each age (year) and gender to the groups. To identify the order of intervention in each treatment group, block randomization was used in this study. A table of random numbers was used to generate the random allocation sequence. One pediatric dentistry resident (S.K.) enrolled participants and one pediatric dentist (E.B.T.) assigned the participants to the interventions. A pediatric dentist (Y.K.) found out about the patient's group just before the treatment session. Due

Table I. Gender and age distribution of the participants

	RG		CG	
	n	**%**	**n**	**%**
Gender				
Male	24	48	26	50
Female	26	52	26	50
Age (years)				
4-5	8	16	14	26.9
6-10	42	84	38	73.1

RG: Robot group, CG: Control group

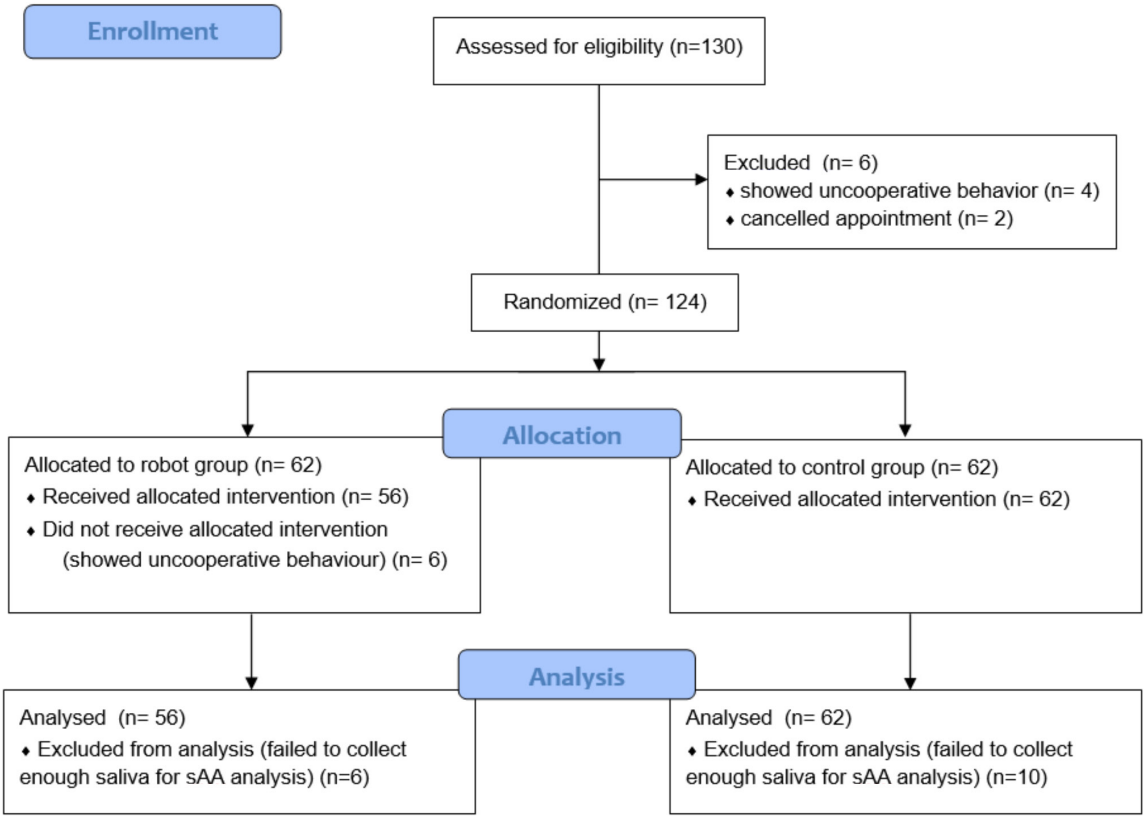


Figure 1. CONSORT flow chart

to the nature of the treatments provided, blinding for FBRS assessment was not possible.

Treatment Procedure

The study protocol was explained to the parents and their written consent was obtained. Pre-treatment questionnaires were asked to the participants.

All children were treated under inferior alveolar block anesthesia. The treatments were performed by the same pediatric dentist (Y.K.). The RG were treated with the robot accompaniment. The CG were treated without the robot. The treatments were completed in the same session.

In the robot group, the distraction technique were achieved by means of the humanoid robot. The robot used in experiments was the NAO, manufactured by Softbank Robotics. NAO is a 58-cm tall robot which is able to perform targeted motor tasks. The robot was programmed to perform the same series of instructions for every patient in order to guarantee that all of the children had the same experience with the robot. The movements of the robot were controlled wirelessly from a computer by using Choregraphe (Aldebaran Robotics, France) software. We prepared the transactions to let the operator run the corresponding commands for each period of the treatment in real time in order to create sequences of behaviors. After each task was defined individually, it was assigned a keyboard input. Some combinations of robot movements were achieved by pressing a single key. With this keyboard interface, the learning time of the operator was minimized. During this period, the system to control the robot was simplified and mistakes were reduced. The NAO audibly and visually distracted the children (Figure 2).

After the dental intervention, the children who were in the robot group were asked "Would you like to see the NAO again in your next appointment?".

Anxiety Status

A series of questionnaires measuring anxiety were administered to each child, before and after their treatment.

FIS is a commonly used scale to determine the dental anxiety levels of children. The children were asked to point at FIS before treatment. This scale consists of five faces numbered from 1 to 5 and ranging from "very happy" to "very unhappy". Each child was asked to point to the face that they related to most closely, according to their feelings at that moment. The questionnaire was repeated after their treatment. FIS is a validated tool for children aged 3-18 years to express their dental anxiety (19).

Behavior Assessment

Frankl's behavior rating scale (FBRS) was used by the dentist to assess each child's behavior (20). It is considered to be one of the most reliable tools developed for the behavior rating of children in dental settings (21). The child's

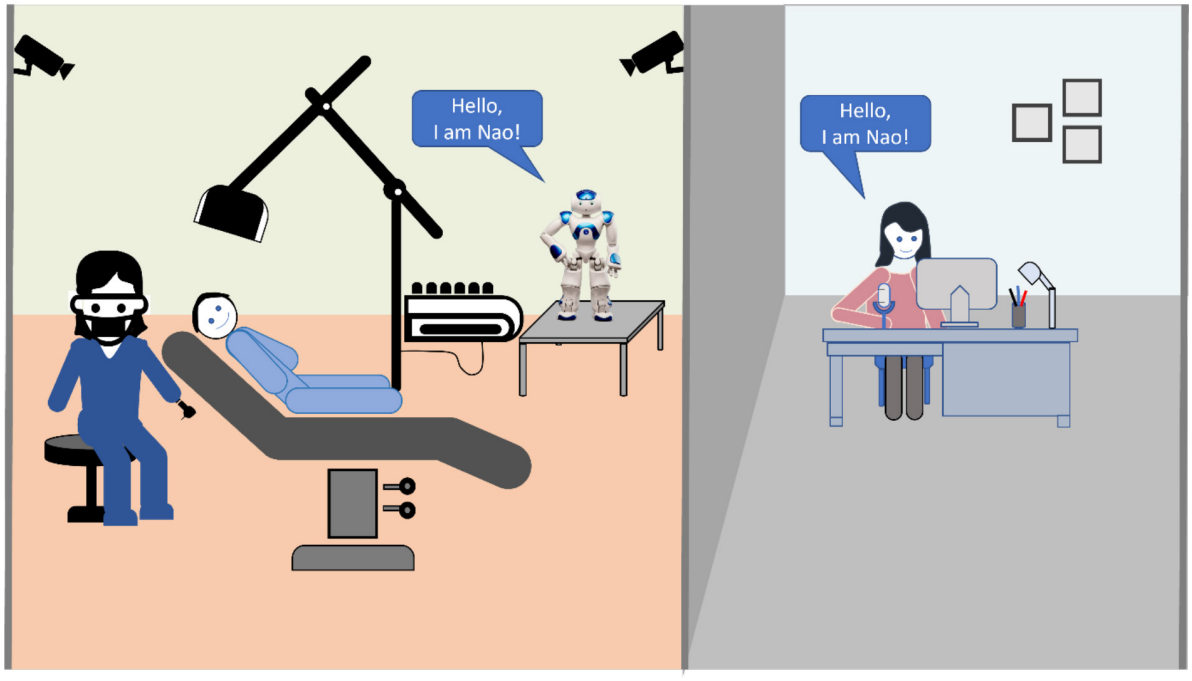


Figure 2. Operation of the robot

behavior is classified by one of the following: definitely negative, negative, positive or definitely positive. The child's behavior was evaluated at their first visit. Children with FBRS scores of 1 were excluded from this study. FBRS was repeated at the end of the treatment sessions.

Physiologic Monitoring

Pulse rate

Monitoring the pulse rate allows for real-time and continuous measurements at different phases of the dental treatment (22). Pulse oximeters were used to measure physiological pulse rates (bpm) before, during and after the treatment.

Salivary amylase activity

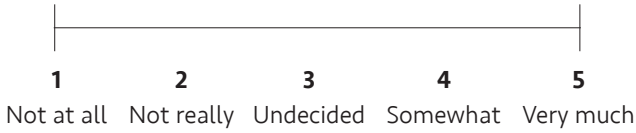
Salivary alpha amylase can be used as a reliable objective tool to measure anxiety during dental treatment (23). Saliva was collected using the "spitting method" (24). Each subject rinsed their mouth with water to reduce contamination of saliva with food debris and waited 5 minutes prior to sampling. Whole mouth saliva from the oral cavity was collected by asking the subjects to sit comfortably in an upright position and drop down their heads, let the saliva run naturally to the front of mouth without stimulating flow by means of orofacial movements. The saliva which accumulated in the floor of the mouth was expectorated into a graduated polypropylene test tube every 30 seconds for a total of 2 minutes. The amount of collected saliva in mL divided by the duration of the collection period, yielding ml/min, was recorded as the mean salivary flow rate.

The saliva samples were collected at three time points as follows: the first saliva samples of the children were collected 5 minutes before the dental treatment (pre-5, measuring the stress of being at the clinic). The patients then underwent dental procedures which lasted around 30 minutes. Right after dental treatment and after 10 minutes of resting (post-10), two new saliva samples were collected (Figure 1). Collection of at least 1 mL was required. After collection, the unprocessed samples were stored at -20 °C until they were analyzed.

Salivary alpha-amylase was measured by a colorimetric assay using 4,6-ethylidene-(G7)p-nitrophenyl-(G1)-D-maltoheptaoside (ethylidene-G7PNP) in an automatic analyzer (Cobas Integra 800, Roche, Basel, Switzerland). The diluted (1:400) saliva samples were assayed.

Children's attitudes towards the robot

After the dental intervention, the children who participated in RG were asked "Would you like to see the NAO again at your next appointment?" Their responses were rated as a minimum of 1 and a maximum of 5.



Statistical Analysis

IBM SPSS Statistics 22 (IBM SPSS, Turkey) was used for the statistical analysis. The Shapiro-Wilk test and the Kolmogorov-Smirnov test were used to check the data distribution. The Mann-Whitney U test and the Student's t-test were used to compare two groups. In-group comparisons of non-normally distributed parameters were tested with the Wilcoxon signed rank test. The chi-squared test, continuity (Yates) correction, and the Fisher-Freeman-Halton test were used to compare qualitative data. Pearson correlation analysis was used to examine the correlation between parameters for normal distribution, and Spearman's rho correlation analysis was used to examine correlations between those parameters with normal distribution. Statistical significance was determined as $p<0.05$. The various age ranges contain children in different development stages, so this variable might have influenced the results. Therefore, we divided the children into two subgroups, namely "preschool" and "school term" children.

Results

Anxiety status

The Mann-Whitney U test was used for FIS comparison between the robot and the control groups, and the Wilcoxon sign test was used for intra-group comparisons before and after treatment.

There was no statistically significant difference between the groups in terms of their mean FIS scores before and after treatment in the 4-5-year-old children. However, the post-treatment FIS scores of the robot group in the 6-10-year-old children was statistically significantly lower than in the control group ($p<0.05$) (Table II).

Behavior assessment

The Mann-Whitney U test was used for FBRS comparison between the robot and the control groups, and the Wilcoxon sign test was used for intra-group comparisons before and

after treatment. The behavior of the children was assessed by one pediatric dentist (EBT) (intra-class correlation coefficient score=0.87). The post-treatment FBRS score was statistically significantly higher in the robot group than in the control group ($p<0.05$) (Table II).

Pulse rate

Student's t-test was used for pulse rate comparisons between the robot and the control groups, analysis of variance was used in repeated measurements before, during and after treatment for the groups, and the Bonferroni test was used for pairwise comparisons within the groups.

There was no significant difference between the robot group and the control group in the 4-5-year-old children. However, for children aged 6-10 years, pulse rates during and after treatment in the robot group were significantly lower than for those in the control group ($p<0.05$) (Table III).

Salivary amylase activity

Student's t-test was used for sAA comparison between the robot and the control groups, analysis of variance in repeated measurements was used for in-group comparisons, and the Bonferroni test was used for pairwise comparisons within groups.

There was no statistically significant difference between the groups in terms of the pre-5, post-1 and post-10 sAA levels in all children. The highest sAA values were observed at the end of treatment in both groups. However, a significant difference was found in the 4-5-year-old children in the control group ($p<0.05$). When comparing the post-treatment values, there were marked decreases in the sAA which were seen to fall to below pre-treatment levels in the robot group ($p<0.05$) (Figures 3 and 4) (Table IV).

Table II. Comparison of the participants' anxiety and behavior before and after treatment

		4-5-year-olds			6-10-year-olds		
		RG	CG	[1]p-value	RG	CG	[1]p-value
		Mean±SD (median)	Mean±SD (median)		Mean±SD (median)	Mean±SD (median)	
FIS	**Before**	2.43±1.51 (2)	2.36±1.69 (1.5)	0.694	2.19±1.23 (2)	2.39±1.37 (2)	0.551
	After	2.29±1.38 (2)	2.93±1.59 (2.5)	0.396	1.31±0.68 (1)	1.84±1.2 (1)	0.019*
	[2]p-value	0.705	0.291		0.000*	0.036*	
FBRS	**Before**	2.57±0.53 (3)	2±0 (2)	0.002*	2.63±0.58 (3)	2.50±0.56 (2)	0.215
	After	3±1 (3)	2.14±0.86 (2)	0.046*	3.52±0.63 (4)	2.74±0.72 (3)	0.000*
	[2]p-value	0.180	0.527		0.000*	0.004*	

[1]Mann-Whitney U Test, [2]Wilcoxon sign test, *p<0.05
RG: Robot group, CG: Control group, FIS: Facial image scale, FBRS: Frankl's behavior rating scale, SD: Standard deviation

Table III. Comparison of the participants' pulse rates before, during and after treatment

	4-5-year-old			6-10-year-old		
	RG	CG	[1]p-value	RG	CG	[1]p-value
Pulse	**Mean±SD**	**Mean±SD**		**Mean±SD**	**Mean±SD**	
Before treatment	110.50±14.71	108.0±12.90	0.682	104.12±14.60	101.57±15.17	0.449
During treatment	120.29±25.70	113.64±13.38	0.440	103.45±16.05	110.92±15.86	0.043*
After treatment	103.86±18.06	104.0±11.24	0.982	95.93±11.90	107.08±13.81	0.000*
[2]p-value	0.013*	0.038*		0.002*	0.024*	
Before/After [3]p-value	0.463	0.855		1.000	0.018*	
Before/Rest [3]p-value	0.947	0.986		0.003*	0.261	
After/Rest [3]p-value	0.008*	0.036*		0.009*	0.560	

[1]Student's t-test, [2]Analysis of variance in repeated measurement, [3]Bonferroni test, *p<0.05
RG: Robot group, CG: Control group, SD: Standard deviation

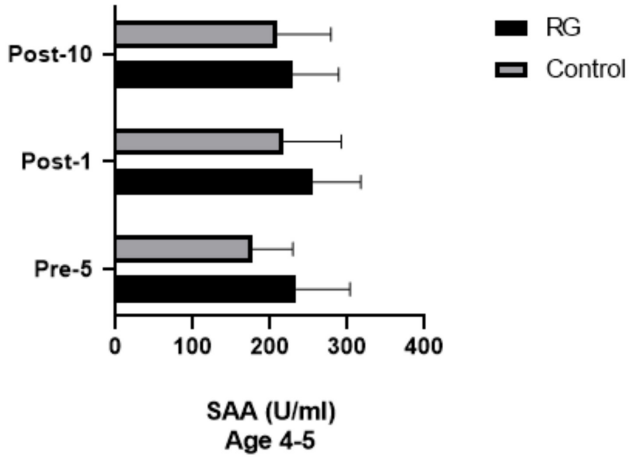


Figure 3. Change of sAA level at three-time measures of children (age 4-5) before and after dental treatment
RG: Robot group, Pre-5: 5 min before the dental treatment, Post-1: immediately after dental treatment, Post-10: 10 min after dental treatment.

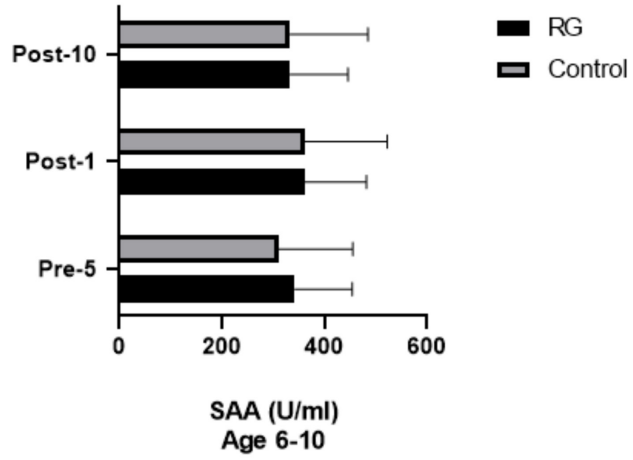


Figure 4. Change of sAA level at three-time measures of children (age 6-10) before and after dental treatment
RG: Robot group, Pre-5: 5 min before the dental treatment, Post-1: immediately after dental treatment, Post-10: 10 min after dental treatment

Table IV. Changes in sAA values in children aged 4-5 and 6-10 years old who underwent dental treatment

	4-5 year-old			**6-10 year-old**		
	RG	**CG**	**[1]p-value**	**RG**	**CG**	**[1]p-value**
sAA (U/mL)	**Mean±SD**	**Mean±SD**		**Mean±SD**	**Mean±SD**	
Pre-5	233.79±69.55	176.96±52.45	0.054	342.27±111.79	310.43±144.83	0.298
Post-1	255.08±62.56	217.9±74.13	0.275	360.6±121.39	360.77±161.53	0.996
Post-10	229.01±59.91	209.48±69.27	0.538	332.52±113.08	332.71±151.92	0.995
[2]p-value	0.002*	0.018*		0.000*	0.000*	
Pre-5/Post-1 [3]p-value	0.085	0.035*		0.000*	0.000*	
Pre-5/Post-10 [3]p-value	1.000	0.023*		0.040*	0.000*	
Post-1/Post-10 [3]p-value	0.048*	1.000		0.000*	0.000*	

[1]Student's t-test, [2]Analysis of variance in repeated measurements, [3]Bonferroni Test, *p<0.05
SD: Standard deviation, RG: Robot group, CG: Control group, Pre-5: 5 mins before the dental treatment, Post-1: immediately after dental treatment, Post-10: 10 mins after dental treatment

Table V. Comparison of the children's willingness to encounter NAO at their next appointment

		Willing to have the NAO in the next appointment		
		Mean±SD	**Median**	**p-value**
Gender	**Boys**	4.79±0.66	5	0.146
	Girls	4.65±0.56	5	
Age (years)	**4-5**	4.0±1.07	4	0.001*
	6-10	4.86±0.35	5	

Mann-Whitney U test, *p<0.05
SD: Standard deviation

Children's attitudes towards the robot

The Mann-Whitney U test was used for comparisons between the genders and age groups to ascertain any differences in the children's eagerness to see the robot (NOA) again.

There was no statistically significant difference between the girls and the boys in terms of wanting the robot accompaniment in their appointments. The 6-10-year-old children were more likely to want to be accompanied by the robot in their appointments than the 4-5-year-olds ($p<0.05$) (Table V).

Discussion

Humanoid robots have been increasingly used in the healthcare system to provide cognitive-behavioral support to patients. In recent years, research on humanoid robots helping to care for the elderly has intensified. Robots may help in the education of children with chronic health problems or special needs such as autism, in the development children's skills, in encouraging children to acquire healthy behaviors, and in making children comfort. However, there are few studies on humanoid robots helping children in the medical field.

The NAO robot is a humanoid robot which can be used in education and therapy. The NAO robot can be used as an educator and as well as a peer of children. It has been used in the classroom to teach new words to children between 3 and 6 years old (25), to assist in speech therapy (12), to adapt children to learn a second language in kindergartens (26), to improve the efficacy of nutritional education (27), and to deliver motivational interviews (28). The NAO robot has mostly been used to improve social behavior and to improve the quality of life in children with autism to date (11,26), and to screen for autism in toddlers, as reported in the literature (29). As NAO has a positive interaction with children, we decided to have NAO to guide, distract and encourage children during their dental treatment.

The distraction method is used to shift the perception of pain to an alternative stimulus. Various tools are used for distraction, from simple interventions to advanced methods such as virtual reality. Two studies were found in which humanoid robots were used as a distraction tool in medical procedures. Beran et al. (30) programmed a robot to distract children during vaccinations and Ali et al. (31) used robot-based distraction therapy in children undergoing intravenous insertion. However, studies on the use of robots to reduce dental anxiety have not yet become widespread.

Virtual reality, one of the most recently developed techniques, is increasingly used in pediatric dentistry to reduce anxiety and pain during local anesthesia or painful procedures such as extraction (32-34). Although no other study has been conducted on the use of humanoid robots in pediatric dentistry apart from ours, humanoid robots, which are complex technology products, can affect pain perception and dental anxiety more effectively than virtual reality because they can be both visually and audibly distracting and socially interactive.

In this study, it was observed that 6-10-year-old children who had dental treatment with the NAO felt happier and had lower pulse rates than the CG children. The children in the RG exhibited more adaptive behaviors than the CG in both age groups. However, in our opinion, better results could be obtained in younger children by performing the dental treatment after a familiarization session with the NAO.

In research examining the biological basis of behavior, salivary measures have emerged that are minimally invasive, easy-to-collect, and relatively inexpensive markers of stress. In our study, saliva was collected using the "spitting method" under supervision. This method is generally accepted as the preferred method in saliva research and it can be used when the flow rate is low; however, it might have some stimulatory effects (35). Unstimulated whole saliva can be sampled by placing absorbent materials such as a cotton sponge and it is one of the few methods for saliva sampling which is easy to perform even at the home. However, swallowing must be avoided and stimulation of salivary flow cannot be completely excluded. The major disadvantage of absorbent materials is the retention of salivary analytes, including sAA, which introduces measurement error (36). Thus, the spitting method seems appropriate enough to be performed by participants during most experimental setups undertaken in the field of psychoneuroendocrinology (37).

The changes in sAA levels are remarkable given that the same mental stress event or age has no impact on sAA levels (16). The parasympathetic nervous system is inhibited when stressed and the sympathetic nervous system is activated, resulting in decreased saliva production and decreased salivary volume. Uncertainties remain about the possible confounding role of salivary flow rate in determining sAA levels. Some reports indicated that stress-induced increases in amylase activities were not correlated with flow rate (16,38). Other studies suggest that valid measurements of sAA require adjustment for the salivary flow rate (15,39). In this study, there were no significant associations observed with sAA levels.

The most powerful aspect of this study is that it was one of the pioneering studies in dentistry in terms of its novel use of social robots in the behavioral management of children. The NAO was well accepted and appreciated by most of the children. At the same time, the possibility of some preschool children not appreciating the NAO should be considered. Although it attracted the attention of most of the children, its high cost and the need for someone knowledge regarding its technology limit the effectiveness of the NAO. One of the potential biases of this study was that behavioral scoring could not be blinded due to the inability to hide the NAO in the RG. Another of the limitations of this study was the inability to obtain sufficient saliva samples for sAA analysis, especially from those children younger than 6 years of age.

Conclusion

As a result of this study, the interaction of children with the NAO during dental treatment was found to be effective in their behavior management. Positive results with the NAO were determined by subjective scales and pulse rate measurements, but no significant difference was found in the sAA levels between the robot and control groups. In the future, robots will be more involved in our daily life and they will be able to accompany and comfort children during their dental treatments.

Ethics

Ethics Committee Approval: This randomized controlled clinical trial was approved by the İstanbul University Faculty of Dentistry Clinical Research Ethics Committee (2017/6) and it was conducted within ethical standards in accordance with the Declaration of Helsinki.

Informed Consent: Informed consent was obtained from all of the children and their parents.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Y.K., Concept: Y.K., S.K., G.İ., E.B.T-İ., Design: Ş.B., G.İ., E.B.T-İ., Data Collection or Processing: Ş.B., G.İ., E.B.T-İ., Analysis or Interpretation: Y.K., Ş.B., G.İ., Literature Search: Y.K., S.K., Writing: Y.K., G.İ., E.B.T-İ.

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

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Original Article

Assessment of the Fear and Anxiety of Children Referred to the Department of Pediatric Dentistry Before and During the COVID-19 Pandemic

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ABSTRACT

Aim: This study aimed to compare the dental fear and anxiety of dental patients aged 6-12 years before and during the coronavirus disease-2019 (COVID-19) pandemic.

Materials and Methods: The first phase of the study was conducted on Group 1 (n=350) before the pandemic and the second phase was conducted on Group 2 (n=350) during the COVID-19 pandemic. Dental anxiety and fear were assessed using 4 scales: the modified dental anxiety scale (MDAS), the modified child dental anxiety scale, the dental subscale of the children's fear survey schedule (CFSS-DS), and the dental fear scale (DFS). In the second phase, participants also filled out a questionnaire related to the COVID-19 pandemic. The data were analyzed using SPSS Statistics 25 (IBM, Armonk, New York).

Results: There were no significant differences between the two groups based on their socio-demographic variables (p>0.05). Scores during the pandemic decreased significantly for the MDAS, CFFS-DS and DFS (p=0.002, p=0.002, p=0.010, respectively). In Group 2, 2% of participants reported that their anxiety increased because of the changes in the dentists' personal protective equipment and 30.9% reported that they were anxious about COVID-19 transmission.

Conclusion: In this study, pediatric dental patients' dental fear and anxiety decreased during the COVID-19 pandemic. Personal protective equipment did not affect pediatric dental patients' dental fear and anxiety.

Keywords: Anxiety, pandemic, COVID-19, dental fear

Introduction

The global burden of the coronavirus disease-2019 (COVID-19) has changed dentists' clinical routines. Initially, the Centers for Disease Control and Prevention (CDC) recommended that dental procedures which are considered high-risk procedures should be limited to emergency dental practice in order to prevent the spread of COVID-19. In addition, patients postponed their oral health needs except for problems which resulted in pain. However, it was accepted that the pandemic would not end in the foreseeable future (1). On June 3rd, 2020, the CDC provided revised guidelines titled ''Interim Reopening Guidance for Dental Settings'' and reported that routine dental procedures should be resumed, albeit with certain protective measures.

However, during the pandemic, it was reported that dental visit frequency decreased due to the fear of transmission, and social behaviors such as nutrition changed

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for the better or for the worse (2-5). The current literature revealed a decrease not only in using dental services, but also in tooth brushing frequencies and the self-perceived need for dental treatment among adolescents (6).

The transmission of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) is associated with droplets, aerosol particles, and infected surfaces, meaning that dentists are at a high risk of transmission and of spreading the disease (7). Therefore, the proper use of personal protective equipment (PPE) is vital for dentists during dental procedures. After the pandemic broke out, dentists raised their protection levels and PPE usage and they felt more uncomfortable compared to their routine practice before the pandemic (4,8). Although pediatric dentists thought that the recommended PPE was not suitable for the non-pharmacological behavioral guidance on pediatric dental patients in the earlier stages of the pandemic, PPE was accepted as vital for preventing the spread of this disease. In addition, personal and equipment hygiene is crucial to prove trustworthiness to the patients and their parents with regards to dental procedures (1). Some of the PPE created a new look for dentists for their pediatric patients, and pediatric dentists continued to have some concerns about children's cooperation during dental procedures (1). These concerns remained as not only a thought, but also as some preventive attempts which were created, such as using posters concerning PPE for pediatric dental patients. Pre-appointment behavioral guidance was suggested to include illustrations concerning the dental visit and the appearance of the pediatric dentists (1). It is known that dental fear and anxiety are exhibited at all ages, but they usually start in childhood (9,10). Therefore, pediatric dentists have a big role in pediatric dental patients' dental histories. Dental fear and anxiety are associated with negative direct and indirect dental experiences, and also increased caries experience (11). Therefore, age-appropriate behavior guidance and pain control may affect the oral health of a child throughout their life.

In the literature, studies about dental fear, stress, and anxiety during the COVID-19 pandemic focused on the fear, stress, or anxiety of dental students, dentists, and dental providers (12-16). There is also a study in which parental fear and distress were evaluated during the pandemic (17). However, when considering dental treatment needs, especially in countries with high patient/disease levels related to caries and their consequences, data on the dental fear and anxiety of the patients during the pandemic period should not be ignored. To the best of our knowledge, there has been no study in the literature to date which compared the dental fears and anxieties of pediatric patients between the pre-pandemic and pandemic periods, with consideration of their socio-demographic factors. The purpose of this study was to compare the dental anxiety and fear of pediatric dental patients before and during the COVID-19 pandemic. The null hypothesis was "there is no significant effect of the pandemic on the dental fear and anxiety of pediatric dental patients".

Materials and Methods

Ethical Consideration

The study protocol was approved by the İzmir Katip Çelebi University Non-interventional Clinical Research Ethics Committee (approval no: 129, date: 27.03.2019). A written informed consent form was obtained from all children and their parents or legal guardians.

Study Design and Sample

This cross-sectional study was conducted on 700 participants aged between 6 and 12 years, who were referred to the İzmir Katip Çelebi University Faculty of Dentistry, Department of Pediatric Dentistry.

In order to determine the sample size, the G*Power (G*Power Ver. 3.1.9.2 Germany) package program was used. For this purpose, considering the data of the studies of Yıldırım et al. (18) and Menziletoğlu et al. (19), it was predicted that there would be a 20% difference between dental fear and anxiety and sociodemographic factors. It was established that a sample size of 350 children would produce a power greater than 95% on a significance level of $p<0.05$. In this context, the first phase of the study was completed on 350 children (Group 1; 217 girls, 133 boys; age range: 6-12 years, mean age: 9.3±1.9 years). After the COVID-19 outbreak, the second phase was conducted on another 350 children (Group 2; 198 girls, 152 boys, age range: 6-12 years; mean age: 9.4±1.9 years) who were referred to the same department.

Data Collection

The data were obtained in two stages; before the COVID-19 outbreak and during the pandemic. The first phase was performed in March and April, 2019 with 350 participants and the second phase of this study was conducted with 350 participants between the dates of September and December, 2020. All 700 participants answered the same questionnaires to evaluate their fear and anxiety. Also, a few questions related to the pandemic were included

in order to understand the patients' perceptions and knowledge in the second phase.

Dental fear and anxiety were assessed using the modified dental anxiety scale (MDAS), the modified child dental anxiety scale (MCDAS), the dental subscale of the children's fear survey schedule (CFSS-DS), and the dental fear scale (DFS). All the scales had been validated in their Turkish versions (20-23).

Statistical Analysis

The data were analyzed using the SPSS 25.0 software (IBM, Armonk, New York). Descriptive statistics of the parameters were given as; number, percentage, mean, standard deviation, minimum, median, and maximum. The normality of the data was tested with the Kolmogorov-Smirnov and Shapiro-Wilk tests. Non-parametric tests were used for non-normally distributed measurements. In the comparisons of quantitative data, the Mann-Whitney U Test was used for the measurements which did not have a normal distribution for differences between two groups. In the comparisons of the scores of more than two groups, the Kruskal-Wallis analysis was used. If there was a difference as a result of the analysis, Dunn's post-hoc test was used for pairwise comparisons. The socio-demographic characteristics between the two samples were analyzed with the Chi-squared test. The reliability of the scales used in this study was tested with the Cronbach alpha reliability analysis. In order to assess the correlation between the scales, Spearman correlation coefficients were calculated. The significance level for all analyses was accepted as $p<0.05$.

Results

The comparisons of the socio-demographic characteristics and dental routines of the two groups are given in Table I. There was no significant difference between the study groups (Group 1, Group 2) in terms of the education levels of the mothers (p=0.486) or fathers (p=0.864), or the family income (p=0.535). While 81% and 82.9% of the mothers' and the fathers' education levels were 8 years or more in Group 1; they were 73.9% and 75.1% in Group 2, respectively (Table I).

There was no statistically significant difference in the frequency of dental attendance (X^2=17,330, p=0.138), dental treatment experience (X^2=38,169, p=0.327), awareness of the planned treatment (X^2=0.266, p=0.606), or the frequency of tooth brushing (X^2=23,302, p=0.078) between Group 1 and Group 2 (Table I).

In this study, anxiety scores during the pandemic decreased significantly according to the MDAS, CFFS-DS and DFS (p=0.002, p=0.002, p=0.010, respectively). However, the decrease in the MCDAS was not statistically significant (p=0.078) (Table II).

In the second phase of this study, when Group 2 answered the questionnaire related to the pandemic, 83.1% of them were aware of the COVID-19 pandemic, 24% of them declared that they were more anxious compared to before the pandemic, and 9.1% of them declared that they were much more anxious than before the pandemic. While only 2% of the patients reported that their anxiety increased because of the differences in PPE, 30.9% reported that their reason was their fear of COVID-19 transmission. In the second PPE specific question, 8.3% of the patients reported that their anxiety increased because of the differences in the PPE during the pandemic (Table III).

In all scales, it was observed that the mean and median of the anxiety values of the participants who had no regular dental attendance were higher than those who had regular dental attendance. The values of MDAS, CFSS-DS, and DFS were significantly higher in those patients who did not have regular dental attendance than in those who attended every six months (Table IV). According to the CFSS-DS and DFS data, it was determined that the dental fears of those who did not have a habit of brushing their teeth were statistically significantly higher than those who brushed their teeth twice a day. When the relationship between regular dental attendance and the COVID-19 pandemic was analyzed by logistic regression analysis, regular dental visits during COVID-19 were 35.71 times less (OR=0.028). During the COVID-19 period, regular tooth brushing (2 or more times per day) was 6.99 times less than before pandemic (OR=0.143) (Table V).

When the anxiety values were compared according to previous treatment experiences, it was determined that the anxiety values of those children who only had tooth extractions were higher than those who previously had had a tooth extraction and filling, had only a filling, or did not receive treatment and this increase was significant in MDAS (X^2=26,129, p<0.01).

In this study, the Cronbach's alpha reliability coefficient values to assess the internal consistency were calculated as 0.75, 0.76, 0.88, and 0.91 for MDAS, MCDAS, CC, and DFS, respectively.

The correlation between the MDAS and MCDAS (r=0.449, p<0.05), MDAS and CFSS-DS (r=0.498, p<0.05), MDAS and DFS (r=0.613, p<0.05), MCDAS and CFSS-DS (r=0.512, p<0.05), CFSS-DS and DFS (r=0.625, p<0.05), and

Table I. Comparison of socio-demographic data of parents and dental routine of the patients between before and during pandemic

		Before pandemic n (%)	During pandemic n (%)	p-value
Education level of mother	Master/PhD	4 (1.1)	4 (1.1)	0.486
	University	95 (27.1)	78 (22.3)	
	High school	89 (25.4)	109 (31.1)	
	Middle school	96 (27.4)	68 (19.4)	
	Primary school	62 (17.7)	79 (22.6)	
	Uneducated	4 (1.1)	12 (3.4)	
Education level of father	Master/PhD	5 (1.4)	8 (2.3)	0.864
	University	66 (18.9)	107 (30.6)	
	High school	97 (27.7)	97 (27.7)	
	Middle school	95 (27.1)	78 (22.3)	
	Primary school	85 (24.3)	56 (16.0)	
	Uneducated	2 (0.6)	4 (1.1)	
Family income (TL)	0-600	17 (4.9)	3 (0.9)	0.535
	600-1000	42 (12.0)	31 (8.9)	
	1000-3000	185 (52.9)	138 (39.4)	
	3000 and higher	106 (100.0)	178 (50.9)	
Regular dental attendance	Once a year	119 (34.0)	16 (4.6)	0.138
	Once every six months	97 (27.7)	156 (44.6)	
	Once every three months	67 (19.1)	30 (8.6)	
	Once a month	60 (17.1)	0	
	None	7 (17.1)	148 (42.3)	
Dental treatment experience	Tooth extraction	37 (10.6)	47 (13.4)	0.327
	Tooth filling	166 (47.4)	121 (34.6)	
	Root canal treatment	50 (14.3)	17 (4.9)	
	Fissure sealant	58 (16.6)	15 (4.3)	
	Fluoride treatment	23 (6.6)	7 (2.0)	
	Space maintainer	0	15 (4.3)	
	Tooth filling and extraction	0	53 (15.1)	
	No treatment	16 (4.6)	75 (21.4)	
Awareness about the planning treatment	Yes	269 (76.9)	190 (54.3)	0.606
	No	81 (23.1)	160 (45.7)	
Frequency of tooth brushing	Three times a day	11 (3.1)	9 (2.6)	0.078
	Two times a day	16 (4.6)	106 (30.3)	
	Once a day	66 (18.9)	129 (36.9)	
	None	257 (73.4)	106 (30.3)	
	Total	350 (100.0)	350 (100.0)	

P-value represented from the chi-square test

Table II. Comparison of MDAS, MCDAS, CFSS-DS and DFS scores between before and during pandemic

		N	Min.	Median	Max.	Mean	SD	U	p-value
MDAS	**Before pandemic**	350	5.00	11.00	23.00	11.58	4.03	52974.500	0.002*
	During pandemic	350	5.00	10.00	23.00	10.61	3.92		
	Total	700	5.00	11.00	23.00	11.09	4.00		
MCDAS	**Before pandemic**	350	8.00	19.00	33.00	18.39	4.74	56550.000	0.078
	During pandemic	350	8.00	19.00	40.00	18.96	5.53		
	Total	700	8.00	19.00	40.00	18.68	5.15		
CFSS-DS	**Before pandemic**	350	15.00	31.00	65.00	33.03	10.43	52825.000	0.002*
	During pandemic	350	15.00	30.00	65.00	30.51	10.89		
	Total	700	15.00	31.00	65.00	31.77	10.73		
DFS	**Before pandemic**	350	20.00	36.00	80.00	37.29	11.52	54321.000	0.010*
	During pandemic	350	20.00	33.00	83.00	35.42	11.93		
	Total	700	20.00	35.00	83.00	36.35	11.76		

U: Mann-Whitney U test statistics, SD: Standard deviation, Min.: Minimum, Max.: Maximum, MDAS: Modified dental anxiety scale, MCDAS: Modified child dental anxiety scale, CFSS-DS: Dental subscale of the children's fear survey schedule, DFS: Dental fear scale

Table III. The number and percentage of answers given at the second stage (during the COVID-19 pandemic) of the study

Questions	Answers	n	%
Do you know about the COVID-19 pandemic?	No idea	59	16.9
	Virus caused disease	291	83.1
Is there a difference in your anxiety during the pandemic compared to before the pandemic?	No difference	52	14.9
	Less anxiety	182	52.0
	More anxiety	84	24.0
	Much more anxiety	32	9.1
What is the reason for the difference in your anxiety during the pandemic compared to before the pandemic visit?	Not respond	185	52.9
	Transmission of the disease	108	30.9
	Personal protective equipment	7	2.0
	None	49	14.0
	News on TV	1	0.3
Did you have difficulty in reaching the doctor/treatment in the pandemic?	Yes	59	16.9
	No	203	58.0
	Partially	88	25.1
Did you worry about coming to the hospital?	Yes	95	27.1
	No	180	51.4
	Partially	75	21.4
Did the change in dentist's clothing in the pandemic raise your anxiety?	Yes	29	8.3
	No	82	23.4
	Partially	239	68.3
	Total	350	100.0

COVID-19: Coronavirus disease-2019

Table IV. Comparison of anxiety and fear scale scores in terms of regular dental attendance during the pandemic period

		N	Min.	Median	Max.	Mean	SD	X^2	p-value	Post-hoc
MDAS	None (1)	148	5.00	11.00	23.00	11.50	4.10	11,649	0.009*	3<1
	Every three months (2)	30	5.00	9.00	17.00	9.83	3.90			
	Every six months (3)	156	5.00	10.00	20.00	9.96	3.63			
	Once a year (4)	16	5.00	10.00	18.00	10.19	3.56			
MCDAS	None (1)	148	8.00	20.00	40.00	19.78	5.24	6,616	0.085	
	Every three months (2)	30	8.00	17.00	30.00	17.80	5.77			
	Every six months (3)	156	8.00	19.00	33.00	18.60	5.65			
	Once a year (4)	16	8.00	17.00	26.00	17.13	5.70			
CFSSDS	None (1)	148	15.00	32.00	65.00	32.94	11.30	12,937	0.005*	3<1
	Every three months (2)	30	15.00	28.50	59.00	29.23	11.94			
	Every six months (3)	156	15.00	28.00	55.00	28.85	9.92			
	Once a year (4)	16	15.00	20.00	47.00	26.63	10.54			
DFS	None (1)	148	20.00	37.00	72.00	38.56	12.40	18,884	0.000*	3<1
	Every three months (2)	30	20.00	29.00	60.00	32.57	9.97			
	Every six months (3)	156	20.00	31.00	76.00	33.08	10.72			
	Once a year (4)	16	22.00	28.50	83.00	34.50	15.86			

X^2: Kruskal-Wallis test statistics, Dunn's post-hoc was used for pairwise comparisons, * indicates p<0.05
Min.: Minimum, Max.: Maximum, SD: Standard deviation, MDAS: Modified dental anxiety scale, MCDAS: Modified child dental anxiety scale, CFSS-DS: Dental subscale of the children's fear survey schedule, DFS: Dental fear scale

Table V. The effect of COVID-19 pandemic on regular dental attendance and regular tooth brushing

		Before pandemic	During pandemic
		N (%)	N (%)
Regular dental attendance (Once a year or more often)	No	7 (2.0)	148 (42.3)
	Yes	343 (98.0)	202 (57.7)
	OR	1 (Reference)	0.028 (0.013-0.061)
Regular tooth brushing (Two times a day or more often)	<2	6 (1.7)	106 (30.3)
	2	344 (98.3)	244 (69.7)
	OR	1 (Reference)	0.143 (0.102-0.200)

Test results of logistic regression analysis; OR: Odds ratio, *p<0.05
COVID-19: Coronavirus disease-2019

MCDAS and DFS (r=0.482, p<0.05) were all moderately positive. There was no correlation between the patients' ages and their anxiety scale results (correlation coincidence between MDAS, MCDAS, CFSS-DS, DFS and age: -0.049, -0.013, -0.091, -0.127 respectively).

Discussion

This study evaluated the dental fear of children aged between 6 and 12 years old before and during the pandemic. The results show that dental pediatric patients' anxieties and fears decreased during the COVID-19 pandemic. This was the first study which compared the dental fear status of the patients in this age group before and after the pandemic. The two groups, which were similar based on their socio-demographic factors, were compared to evaluate the effects of the pandemic on their dental anxiety.

The decrease in the anxiety levels in the pandemic era may be explained by the decrease in the number of patients at the clinic. A less crowded, less noisy, and calmer environment might have decreased the anxiety levels.

This result was compatible with the result of a previous study which reported that patients' dental anxiety was associated with their waiting time before treatment (24). It has also been shown that the characteristics of the clinical environment are effective in the clinic experience of young people (25).

The participants of this study were school-age children so, when asked in the second phase of the study, most of them were aware of the COVID-19 pandemic. Less than half of participants reported feeling more anxious than their pre-pandemic dental experience levels. Also, more than half of them reported that they were less anxious compared to their pre-pandemic dental experiences. It was observed that the declarations of the participants were in accordance with the results of their dental anxiety scales. In a study conducted in Brazil, pediatric dentists reported that their routine treatment practices had changed, and they had reduced the use of high-speed instruments (8). In our clinic, a decrease in the frequency of using high-speed instruments may also have been effective on reducing dental anxiety and fear during the COVID-19 period.

Few participants (8.3%) reported that the changes in PPE of the clinicians increased their anxiety, and some of them (30.9%) reported that their anxiety increased due to fears of COVID-19 contamination. According to the results of this study, despite the estimations and hesitations of many clinicians, it was observed that the levels of fear and anxiety of children did not increase due to the changes in PPE and the precautions taken as a result of the pandemic.

Uncontrollability and unpredictability have been shown to be associated with dental fear (26). Non-invasive dental procedures can improve a patient's tolerance to more invasive procedures in following appointments (11,27,28). However, Corcoran et al. (26) reported that dental fear frequency was increased in adolescents with cleft lip and palate who had several dental procedures throughout their childhood. They attributed this situation to the low effectiveness of anesthesia (for patients with cleft involving lip) due to scar formation and due to the excessive treatment procedures which children with cleft lip and palate undergo (26). In this study, the fear and anxiety values of those patients who only had a tooth extraction history were higher (according to their MDAS and DFS values) compared to those who had other dental procedures or who had both fillings and extractions. Therefore, the results of this study showed the importance of delaying invasive procedures, such as elective extraction, to improve the child's cooperation.

It has been reported that the dental fear of the patients who did not have regular dental visits was increased compared to those patients who had regular dental visits (29,30). Similarly, in this study, the anxiety values of irregular attendees were higher than those of regular attendees. The least anxiety scores were assessed from those participants who has dental attendance every 6 months. We can explain the insignificant difference in anxiety levels between those with regular attendance every 3 months and those with irregular dental attendance by the fact that those patients with a high risk of caries needed more frequent dental visits. The fact that experience of treatment for caries and the need for more invasive treatments were associated with increased dental fear and anxiety supports this idea (11,26).

It has been reported that students' physical activity and their oral hygiene habits deteriorate during holidays and periods of disruption of daily routines compared to school time (31-33). In a cohort study evaluating the psychosocial and behavioral changes before and during pandemic among adolescents, it was reported that tooth brushing and oral health perception decreased significantly during the pandemic. They explained that this decrease might be associated with the extraordinary situation of pandemic (fear associated with COVID-19 related death etc.) (6). Consistent with the results of these studies, we determined a 6.99 and 35.71 fold decrease in regular tooth brushing and dental attendance respectively when comparing the periods before and during the pandemic.

In this study, no correlation was found between dental anxiety and age. Although there are many studies which have reported that dental fear and anxiety decreased with age, there are conflicting studies stating that it fluctuates with age or that it is not related to age (11,30,34-36). These conflicting results may be explained by variables such as differences in the study designs, the outcome measurements, the oral health behavior of the subjects, their dental pain, and/or differences in culture (11,37).

Study Limitations

This study was conducted with a new sample in the second phase instead of re-calling the previous participants. The same participants could not be recalled due to ethical reasons because there was still a risk of COVID-19 transmission but it was thought that including new participants who actually needed dental intervention and were referred to the clinic was reasonable. To mitigate any possible confounding factors in terms of this issue, we included a sample with similar sociodemographic characteristics. Caries and their results were not assessed,

and this can be considered as a limitation of this study due to the relationship between the treatment experiences for carries and the dental fear and anxiety of the patients (11).

Conclusion

In spite of the fear of COVID-19 transmission, dental fear and anxiety decreased during the pandemic. The changes in the dentist's appearance related to their PPE did not appear to have increased dental fear and anxiety in pediatric patients. Controlling environmental factors and decreasing the use of high speed instruments may have played a role in reducing the dental fear and anxiety levels of dental pediatric patients.

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Ethics

Ethics Committee Approval: The study protocol was approved by the İzmir Katip Çelebi University Non-interventional Clinical Research Ethics Committee (approval no: 129, date: 27.03.2019).

Informed Consent: All participants and their legal guardians were informed about this study and signed informed consent forms.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.K, F.Ç.D., Design: F.Ç.D., E.K., Data Collection or Processing: F.Ç.D., S.E.K., Analysis or Interpretation: F.Ç.D., Literature Search: F.Ç.D., E.K., Writing: F.Ç.D., E.K.

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Case Report

Garre's Osteomyelitis of the Jaw in a Child: Report of a Case Treated with Colchicine

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ABSTRACT

Garre's osteomyelitis is a rare chronic inflammatory disease with reactive peripheral bone formation due to low-grade local infection. Here, we present a 12-year-old female with chronic osteomyelitis and proliferative periostitis with no definite source of infection, such as caries or periodontitis. The patient had a history of 4-5 hospitalizations with the same symptoms intermittently over the previous two years at the hospital which referred her to our hospital. The patient had undergone a biopsy at the referring hospital, and she was referred to our hospital with a histopathological diagnosis of osteoid osteoma. Physical examination showed a unilateral swelling in the right mandible at admission to our hospital. Since we could not exclude the diagnosis of bacterial osteomyelitis, antibiotics were continued. Periapical radiography, magnetic resonance, computed tomography, and clinical features supported the diagnosis of Garre's osteomyelitis, so antimicrobial therapy was discontinued. Her biopsy materials were re-examined by the pathologist at our hospital, and Garre's osteomyelitis was considered. Non-steroidal anti-inflammatory drugs were started. We added colchicine treatment because she failed to achieve remission, and normal facial symmetrical morphology was not achieved in the two-month follow-up period. However, the symptoms regressed within one year, and the swelling disappeared.

Keywords: Garre's osteomyelitis, mandibular, children

Introduction

Chronic osteomyelitis with proliferative periostitis is a rare osteomyelitis characterized by periosteal reaction and new bone formation and it is traditionally known as Garre's osteomyelitis (1). The first cases affecting the jaw were reported in 1948 by Berger, and Pell described them in 1955. It generally originates from a low-virulence infection and it is characterized by chronic non-suppurative proliferative osteomyelitis associated with new bone formation (2).

Common sources of jaw infection include periapical periodontitis, periodontitis, fractures, and dental caries associated with non-odontogenic infections (3). Garre's osteomyelitis mainly occurs in young patients and often affects the mandibular trunk unilaterally (4,5). The premolar and molar regions of the mandible are most affected.

The lesion is characterized by local thickening of the periosteum with a reactive deposition of new cortical bone and periosteal osteoid. Clinically, this reactive process can be seen with a firm swelling on the jaw followed by facial

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asymmetry. Although its clinical symptoms are variable, the lesions are usually asymptomatic (6).

Imaging findings of the jaws in Garre's osteomyelitis are bone hyperplasia and destruction. Histological examination showing new bone formation under the periosteal layer is a characteristic disease feature. Extraction of the offending tooth, antibiotics, and non-steroidal anti-inflammatory drugs (NSAIDs) were reported as the most common treatment options (4,7).

Here, we present a case of chronic osteomyelitis with proliferative periostitis in a child.

Case Report

A 12-year-old female was referred to our department in February, 2021 due to persistent pain, jaw swelling, and difficulty in eating. The patient was previously healthy with no known systemic illnesses/allergies and had not received any medications apart from frequent antibiotics and NSAIDs for painful episodes of jaw swelling. No trauma/dental history was reported. There was no significant family history.

She had reported recurrent painful episodes with swelling in the right mandible over the prior two years. She had been hospitalized with similar symptoms 4-5 times in the past, and intravenous antibiotics had been given for suspected acute osteomyelitis. The ultrasonography performed in the hospital she was referred from showed soft tissue involvement, edematous, and hyperemia in the subcutaneous area and the right buccal region. Magnetic resonance imaging (MRI) showed expansion of the intramedullary bone, which extended slightly towards the body part of the bone, and bone marrow edema accompanied by cortical irregularities in the ramus of the mandible on the right and an inflammatory process surrounding the soft tissues. Intravenous ceftriaxone and clindamycin treatment were administered due to radiological findings indicating osteomyelitis. A biopsy was performed because of persistent symptoms despite receiving appropriate treatment for 15 days, and the histopathological diagnosis was reported as "osteoid osteoma" at the hospital which the patient was referred from.

On the first examination at the pediatric infectious diseases department of our hospital, the patient was afebrile, and neither tachycardic, nor tachypneic. Physical examination showed unilateral swelling on the right mandible, and facial asymmetry was noticed (Figure 1); however, no tenderness, erythema, or intraoral signs of gingival or periodontal infection were observed. The following were the results of the patient's laboratory tests: total leukocyte counts $9.09x10^3/\mu L$ (neutrophil 60%, lymphocyte 33%, monocyte 4.1%), hemoglobin 12.5 g/dL, platelet count: $284x10^3/\mu L$, C-reactive protein: 0.6 mg/L, lactate dehydrogenase: 171 U/L, erythrocyte sedimentation rate: 21 mm/hour, and her liver and kidney function tests were normal. Ampicillin/sulbactam treatment was also initiated due to the suspicion of bacterial osteomyelitis. The basic immunological tests and oxidative burst activity were normal. Viral markers showed past cytomegalovirus and rubella infections. Blood cultures were negative.

Periapical radiography demonstrated no findings of periapical periodontitis or fractures (Figure 2). The mandibular radiography (Figure 3) showed an "onion skin" appearance of the distended cortical plate buccal and inferior tooth. Computed tomography imaging showed bony expansion, diffuse sclerosis, cortical thinning, and periosteal reaction involving the right mandibular body, angle, and ramus (Figure 4). MRI revealed an abnormal bone marrow signal compatible with edema. Increased

Figure 1. Pre-treatment extra-oral photographs; (A) lateral view; (B) Frontal view; (C) 2 months later

signal on T2-weighted images and contrast enhancement on fat-saturated T1-weighted images were present in the surrounding soft tissue, indicating edema and inflammation (Figure 5). These imaging findings were highly suggestive of Garre's sclerosing osteomyelitis. Biopsy material testing performed in the previous hospital was re-evaluated by the pathologist in our hospital and it showed new bone formation with periosteal reactivity, a significant inflammatory process.

Regarding the histopathological and radiological findings, Garre's osteomyelitis was considered. Antibiotic therapy was discontinued. Non-steroidal anti-inflammatory treatment was started. The pain disappeared on the 16th day of hospitalization, and the patient was discharged. Since the swelling continued through to the follow-up two months later, colchicine was added. Six months after her discharge, the swelling had regressed by 60-70%. At the 1-year follow-up, the patient was asymptomatic with no

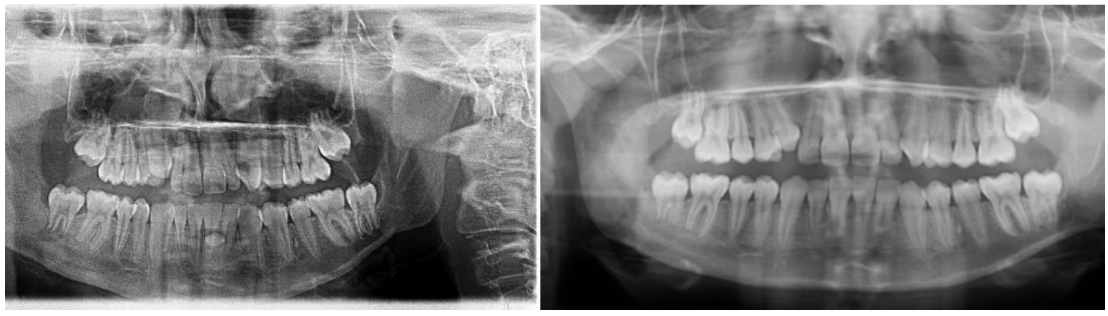

Figure 2. Panoramic radiograph showing the no findings of periapical periodontitis or fractures

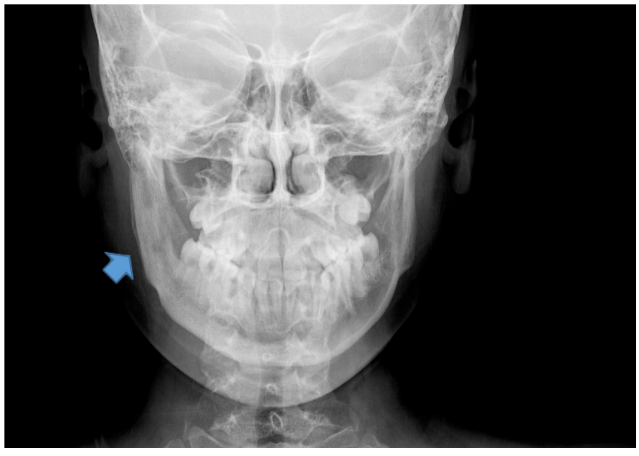

Figure 3. No findings of periapical periodontitis or fractures appearance of the distended cortical plate buccal and inferior tooth

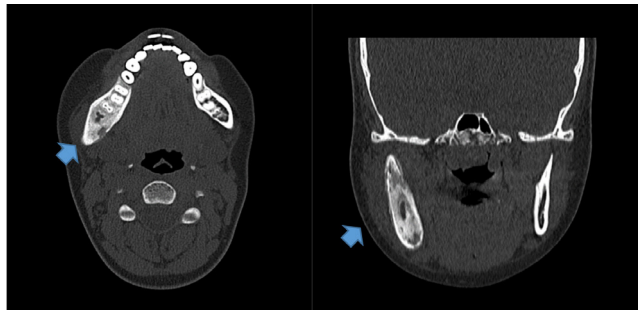

Figure 4. Axial (a) and coronal reformatted (b) CT images show bony expansion, cortical thinning, and periosteal reactions at the right mandibular body, angle, and ramus

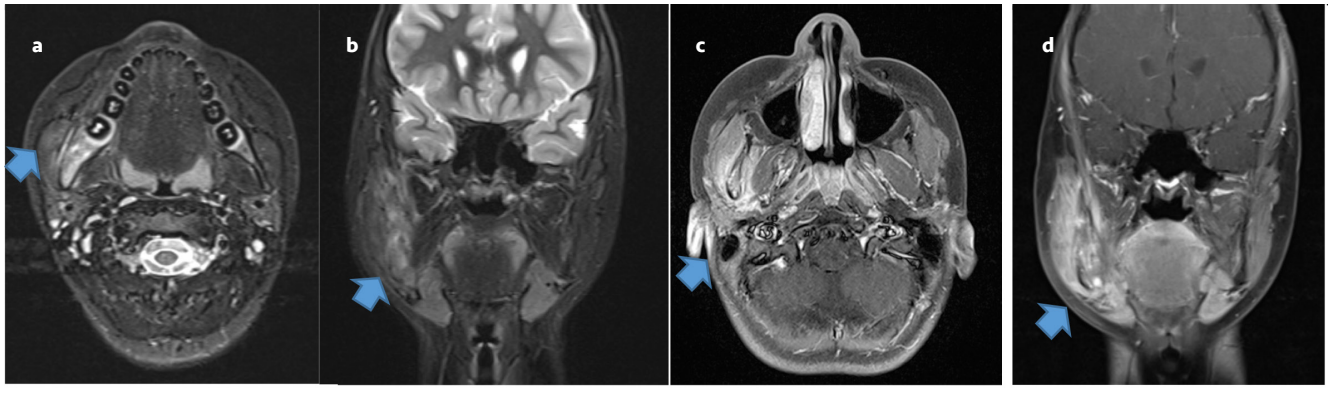

Figure 5. Fat-saturated T2-weighted axial (a), coronal (b) images and contrast-enhanced fat-saturated T1-weighted axial (c), coronal (d) images show bony expansion, bone marrow edema, and soft tissue inflammation adjacent to the lesion

palpable swelling. Written informed consent was obtained from the parents to publish their child's pictures.

Discussion

We report a case of Garre's osteomyelitis in a 12-year-old female whose age was in the range where this disease is common. Garre's osteomyelitis affects the mandible more than the maxilla and involved the unilateral mandible (5). Consistent with the literature, unilateral mandibular involvement was detected in our case.

Dental problems and inflammatory diseases have been primarily reported in the etiology. The pathogenesis of Garre's osteomyelitis has been suggested as being because the periosteum has more osteogenic potential during the growth phase of the jawbone in response to a stimulation of an inflammatory process in very young patients (especially <15 years). The severity and variability of symptoms are determined by various factors, including the organism's virulence, the host's immunity, and the person's underlying systemic condition (4,8). No periapical or periodontal pathology, history of trauma, or underlying systemic diseases were noticed in our case.

The clinical features are episodic non-progressive, insidious onset, and localized pain. Its duration is highly variable, lasting several months or several years. The lesions may be asymptomatic, persistent, or intermittent. In general, the function of the affected bone is preserved (9). In the present case, multiple episodes were reported with an adverse effect on the quality of life. There was a long-term history in our case. The function of the bone was preserved.

Radiologic studies in Garre's osteomyelitis have shown the presence of bony laminations, called "onion skin" appearance (10). In our case, radiological studies supported the diagnosis of Garre's osteomyelitis, showing bony expansion, diffuse sclerosis, cortical thinning, and periosteal reaction.

The diagnosis of Garre's osteomyelitis is usually based on clinical and radiological findings. However, a biopsy can be used for a definitive diagnosis when clinical and radiological findings are not pathognomonic. In our case, a biopsy was performed because of initial non-specific findings.

Treatment options include antibiotics, anti-inflammatory drugs, colchicine, steroids, conservative therapy, and surgery (4,7). Indications for antibiotic treatment include fever of more than 100 °F (37.8 °C), malaise, lymphadenopathy, trismus, cellulitis, and rapid soft tissue swelling associated with infections. Since the patient presented here was referred to our hospital with a preliminary diagnosis of osteomyelitis, antibiotics were administered until the diagnostic studies were completed. When Garre's osteomyelitis was diagnosed, this treatment was discontinued because the patient had no dental pathology, fever, cellulitis, or erythema. As the swelling did not regress with NSAID treatment, colchicine was added, and the patient recovered without surgery.

In conclusion, in this case, radiological findings and the recovery period of Garre's osteomyelitis, which is rare, are discussed. It should also be kept in mind that remission may occur with colchicine treatment without surgery when there is no response to NSAID treatment.

Ethics

Informed Consent: Written informed consent was obtained from the parents to publish their child's pictures.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Case Report

Varicella-zoster Virus Encephalitis in an Immunocompetent Child Without Vaccination

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ABSTRACT

Chickenpox, the primary infection of the Varicella-zoster virus (VZV), is usually a benign, self-limiting disease and it rarely causes severe complications. Encephalitis is a rare neurological complication of VZV in previously healthy children. We report on an immunocompetent child without vaccination diagnosed with VZV encephalitis who was treated with acyclovir and methylprednisolone and recovered completely.

Keywords: Varicella-zoster virus, encephalitis, vaccination, immunocompetent, children

Introduction

The Varicella-zoster virus (VZV) is an enveloped double-stranded DNA alphaherpesvirus which primarily causes chickenpox, a highly contagious airborne disease. Chickenpox is an acute infectious disease which usually affects children without vaccination and has a self-limiting course in younger children (1,2). However, on rare occasions, it can cause severe complications such as neurological complications (3). VZV can affect the central and peripheral nervous system and cause meningitis, encephalitis, cerebellitis, acute myelitis, stroke, optic neuritis, vasculopathy, or myelopathy. These central nervous systems (CNS) complications can follow both primary infections and the reactivation of VZV (1-4). Encephalitis is another neurological complication of primary VZV infection, and in previous reports, the incidence of encephalitis associated with VZV ranged from 0.5 to 2.4% in children (4,5). VZV encephalitis typically occurs in immunocompromised patients with human immunodeficiency virus (HIV)/acquired immune deficiency syndrome, transplantation, or autoimmune disease. However, VZV encephalitis can occur in immunocompetent children in rare cases (2,3). Herein, we report on an 11-year-old immunocompetent child with VZV encephalitis who was treated with acyclovir and methylprednisolone and completely recovered without any neurological sequelae.

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Case Report

A previously healthy 11-year-old male was admitted to the emergency department with a 4-day history of vomiting and a 2-day history of fever, headache, dizziness, and weakness with inability to walk. The patient had been seen at a different hospital two days prior due to vomiting and was discharged to home after symptomatic treatment. He had a history of chickenpox 15 days prior. He had no vaccination history for VZV. On examination, he had multiple small scars, some with scabs and a few vesicular eruptions across his whole body as a manifestation of the recent varicella infection (Figure 1). The general examination, including his vitals, was found to be within normal limits. His neurological examination revealed lethargy, slow speech, and cerebellar ataxia. Motor examination revealed normal tone and nearly normal power (4/5) in both his upper and lower limbs. Deep tendon jerks were increased in both his lower limbs, and his plantar reflex was flexor bilaterally. Sensory examination was normal. No signs of meningeal irritation and no other cranial nerve abnormality were detected. Cefotaxime and acyclovir were administered for suspected CNS infection. Laboratory tests revealed a leukocyte count: 12.800/mm^3, a neutrophil count: 10.860/mm^3, a lymphocyte count: 1.110 mm^3, a platelet count: 326.000/mm^3, C-reactive protein: 0.7 mg/dL, and his biochemical parameters were normal except for high creatinine (serum creatinine 1.19 mg/dL). Abdominal ultrasonography revealed nephropathy, and acyclovir was administered according to renal dosage. Coronavirus disease-2019 (COVID-19) polymerase chain reaction (PCR) was negative. Cranial computed tomography and arterial-venous cranial angiography were normal. Contrast-enhanced craniospinal magnetic resonance imaging (MRI) showed non-specific millimetric hyperintensity in the right frontal region. A lumbar puncture was performed, cerebral spinal fluid (CSF) was clear in appearance, and its pressure was normal. Laboratory examination of CSF revealed no cells, a normal protein level of 14.6 mg/dL, and a normal glucose level of 94 mg/dL. A multiplex PCR test for CSF was positive for the VZV. Blood serology tests were positive for VZV immunoglobulin (Ig) M and IgG. Bacteriologic culture of CSF and blood were negative. A sleep electroencephalogram (EEG) was performed on day 2 of admission. It showed a moderate amplitude of theta delta waves, evaluated as minimal cerebral dysfunction. According to the clinical and laboratory findings, this clinical course was diagnosed as encephalitis associated with the VZV. On the 3rd day of admission, he had hypertension, bradycardia, and worsening consciousness. On eye examination, he had no papilledema. A second craniospinal MRI was performed which only showed mucosal thickening in the right maxillary ethmoid and sphenoid sinuses. Due to his rapid clinical worsening, autoimmune encephalitis triggered by a viral infection could not be excluded. For these reasons, 2 g/kg intravenous immunoglobulin (IVIG) and 2 mg/kg/g methylprednisolone were administered, and the acyclovir dosage was increased to normal. His consciousness improved within one day, and his neurological examination was completely normal after seven days. After his bacterial cultures were negative, cefotaxime was discontinued on the 7th day. His anti-N-methyl-D-aspartate receptor (NMDA) receptor panel was negative for a blood sample. His immunoglobulins and lymphocyte panel were checked and found to be normal. In addition, the patient's HIV serology was negative. On the 14th day of admission, a second lumbar puncture was performed, CSF was clear in appearance, and its pressure was normal. Laboratory examination of CSF revealed no cells, a normal protein level of 17.5 mg/dL, and a normal glucose level of 61 mg/dL. The multiplex PCR test of CSF was negative for VZV, and acyclovir was discontinued after 14 days. After six days, methylprednisolone was tapered down and discontinued after 30 days. The patient completely recovered and had no neurological complications in the follow-up.

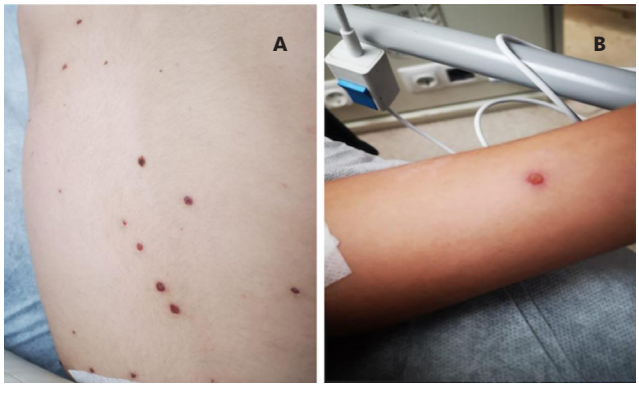

Figure 1. On admission, the patient had multiple small scars, some with scabs (A), and a few vesicular eruptions (B) on his whole body as a manifestation of a recent varicella infection

Discussion

Chickenpox, the primary infection of VZV, is a usually benign and self-limiting childhood disease. However, it rarely causes life-threatening complications affecting hematological, neurological, respiratory, cutaneous, and/or gastrointestinal systems. These complications are more common in patients with immunosuppression,

T-cell defects, genetic mutations such as ribonucleic acid polymerase (POL) III mutations, underlying diseases, such as chronic cutaneous or pulmonary diseases, and in adults (2,3). Neurological involvement in healthy children following VZV is rare (4). We report on an immunocompetent child without vaccination diagnosed with VZV encephalitis who was treated with acyclovir and methylprednisolone, and recovered completely.

VZV is a human neurotrophic virus which remains latent in the nervous tissue (1). The neurological complications of VZV can be caused by the primary infection or virus reactivation (6). The pathogenesis of neurological complications was reported as direct VZV infection of affected tissue, persistent inflammation, and virus-induced hypercoagulability. However, the pathogenesis of VZV encephalitis is still unclear, and the possible mechanism of VZV encephalitis has been associated with vasculopathy and/or radiculitis (1,7).

VZV encephalitis can be diagnosed with clinical, laboratory, or radiologic findings. VZV encephalitis usually presents with symptoms of headache, altered mental status, and the characteristic rash of varicella. However, VZV infections can cause CNS complications with or without rash (1). The laboratory findings of CSF can be normal or include pleocytosis (7). PCR analysis of CSF for diagnosis has high sensitivity and specificity. However, a negative test result does not exclude the diagnosis of VZV encephalitis (7,8). In patients with negative cerebrospinal fluid PCR results, detecting CSF VZV IgM antibodies can be helpful in diagnosing encephalitis (8). Cranial MRI can show encephalitic changes; however, there is no typical presentation, and MRIs are often normal (6). The electroencephalogram may be normal or show nonspecific abnormalities such as slowing basal activity (2,7). In our case, VZV PCR was positive in the CSF. Cranial MRI revealed nonspecific millimetric hyperintensity in the right frontal region, and his EEG showed minimal cerebral dysfunction. All these findings were compatible with VZV encephalitis.

There are no specific guidelines for the treatment options for VZV encephalitis in immunocompetent children. Based on case reports and small series, acyclovir (10-15 mg/kg intravenously every 8 hours) is the treatment of choice and its recommended duration is 10-14 days. In immunocompromised patients, the treatment is recommended to be prolonged to 21 days (8). In addition to acyclovir, some experts recommend corticosteroids for their anti-inflammatory effects (1,2,8). Early diagnosis and intravenous acyclovir treatment may result in clinical benefits and prevent neurological complications and sequelae (2). Our case received acyclovir for 14 days and methylprednisolone for 30 days and completely recovered.

Several primary immunodeficiencies have been reported to predispose patients to severe varicella infections. Secondary immunodeficiencies, such as HIV infection, immunosuppressive medication, etc., can also predispose individuals to severe VZV infection in addition to primary immunodeficiencies (3). For these reasons, evaluating the immune status of patients with a severe varicella infection is essential. In addition to the standard immunodeficiency tests, detailed genetic tests for primary immunodeficiency can be planned for these patients. Our patient's immunoglobulin levels and lymphocyte panel were normal, and he had no known secondary immunodeficiencies.

VZV encephalitis can cause irreversible brain damage, resulting in mental retardation, stroke, giant cell arteritis, and granulomatous aortitis (6). In very rare cases, it has been reported that VZV encephalitis can trigger autoimmune anti-NMDA receptor immunoreaction and cause the occurrence of NMDAR antibodies leading to encephalopathy (9). Anti-NMDAR encephalitis following the Herpes simplex virus is a more frequently described condition. However, in the literature, only four adult patients with VZV-associated anti-NMDAR encephalitis have been reported to date (9-12). This disease is characterized by encephalopathy, behavioral changes, psychosis, memory deficits, seizures, abnormal movements, autonomic dysfunction, and coma. It is more common in young women, and after a prodromal period, it often begins with sudden behavioral and personality changes. These symptoms are followed by seizures, decreased levels of consciousness, abnormal movements, autonomic instability, and hypoventilation (11). The diagnosis can be made by CSF anti-NMDA antibody positivity (9). Acyclovir and immunomodulatory treatments such as corticosteroids, IVIG, and plasma exchange can be used in its treatment (9-12). Our case had a rapid clinical worsening, and autoimmune encephalitis triggered by a viral infection could not be excluded, and for these reasons, IVIG and methylprednisolone were administered. Due to a limited CSF sample, we could not perform a cerebrospinal fluid NMDAR analysis to exclude this diagnosis. We could only perform the test of the NMDAR panel on a blood sample, and this was negative.

Chickenpox is a vaccine-preventable disease. Worldwide, there are several formulations of varicella vaccines, and all contain live attenuated VZV. Streng et al. (13) evaluated 1.263 varicella-associated pediatric hospitalizations after a VZV

vaccination program had begun in Germany. They reported that the incidence of varicella-associated neurologic complications in children decreased by approximately 60% during the first seven years following the recommendation for universal VZV vaccination. Our case had no vaccination history for VZV, and the development of severe complications in our patient may be due to his lack of vaccination.

In conclusion, although VZV infections are generally mild and self-limiting in children, life-threatening complications and even death can occur. VZV encephalitis is a rare neurological complication of VZV infection in previously healthy children, and vaccination can prevent these severe complications. We reported on a rare pediatric case of VZV encephalitis who completely recovered with acyclovir and methylprednisolone treatment. During the COVID-19 pandemic, other viral infections and their rare complications should be kept in mind, and we should start early treatment in order to prevent possible complications and squeals.

Ethics

Informed Consent: Written informed consent for presenting clinical data and using photographs in this manuscript was obtained from the patient's parents.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: G.G.Ö., A.A.K., F.Y.A., Ü.Y., Design: G.G.Ö., A.A.K., F.Y.A., Ü.Y., Data Collection or Processing: G.G.Ö., A.Ö., M.Y.Ç., M.G., F.Y.A., Ü.Y., Literature Search: G.G.Ö., A.Ö., M.Y.Ç., F.Y.A., Ü.Y., Writing: G.G.Ö.

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