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Original Articles

Case Reports

Turkish Journal of Pediatric Disease

Original Article

The Impact of Human Parainfluenza Virus on Child Health: A Clinical Study

Furkan KALAYCI[1], Ece KARAKÖSE[1], Ayça ÇIRAK[1], Metin YİĞİT[1,2]

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ABSTRACT

Objective: This study aims to identify the clinical characteristics of Human Parainfluenza Virus (HPIV) infections in children, evaluate morbidity and mortality rates, and investigate the impact of chronic diseases on the course of these infections.

Material and Methods: The research was conducted retrospectively and cross-sectionally on children aged 0-18 who tested positive for HPIV in the respiratory viral panel at Ankara Bilkent City Hospital Children's Hospital between August 2019 and July 2023. Patients with multiple virus positivity were excluded from the study.

Results: The study included 160 patients, of whom 61.2% were male and 38.8% were female. The most common presenting symptoms were cough (66.3%) and fever (52.5%). Of the patients, 41.2% were treated as inpatients, and 19.6% received care in the intensive care unit. The need for invasive or noninvasive mechanical ventilation was observed in 10% of the patients. There was a statistically significant association between the presence of lung infiltration and chronic disease with hypoxia ($p < 0.001$).

Conclusion: While HPIV infections are generally mild, they can lead to significant morbidity and the need for intensive care in children with chronic diseases. These findings highlight the necessity for careful clinical evaluation and close monitoring of children with HPIV infections. The study's results may contribute to the management and treatment strategies for HPIV infections in the pediatric population.

Key Words: Child, Parainfluenza virus, Pneumonia, Upper respiratory tract infection

INTRODUCTION

Human Parainfluenza Virus (HPIV) is an enveloped, negative-sense, single-stranded RNA virus belonging to the Paramyxoviridae family (1). It was first isolated from children with croup in the late 1950s (2). Today, it has been shown to constitute a significant portion of lower respiratory tract infections in children (3).

HPIV infections typically present with symptoms of upper respiratory tract infections, including fever, cough, runny nose, and sore throat (4). However, HPIV can cause severe respiratory diseases in young children or those with comorbid conditions (5). It is reported as the second most common cause of respiratory tract infections in children under five years of age, after RSV viruses (5–7).

This study aimed to determine the clinical features, morbidity, and mortality of HPIV infections, with a particular focus on assessing the severity of outcomes in children with chronic diseases.

Conflict of Interest : On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics Committee Approval : This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Bilkent City Hospital, Ethics Committee No. 1 (24.04.2024/ 140).

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MATERIALS and METHODS

Our study was designed as a retrospective, cross-sectional analysis. It included all children aged 0-18 years who presented to Ankara Bilkent City Hospital's Children's Hospital between August 2019 and July 2023 and tested positive for HPIV on the respiratory viral panel. Patients with simultaneous positivity for other viruses were excluded from the study.

Respiratory pathogens were identified using a multiplex real-time PCR assay (Rotor-Gene Q, QIAGEN, Germantown, MD). The admission dates and seasons, presenting complaints, history of chronic diseases, laboratory values, lung infiltrations, hypoxia status, need for hospitalization, hospitalization settings (ward or intensive care), and requirements for mechanical ventilation (invasive or non-invasive) of patients who tested positive for HPIV were retrospectively reviewed. Patients with missing clinical or laboratory data were excluded.

The study population was divided into three groups based on the presence of chronic diseases. The first group comprised individuals with primary or secondary immunodeficiencies, the second included those with chronic lung diseases, and the third consisted of patients without respiratory-affecting chronic diseases or those free from any chronic conditions.

Statistical analyses were conducted using Statistical analyses were conducted using IBM Statistical Package for the Social Sciences, version 23.0 (SPSS Inc., Armonk, NY, IBM Corp., USA). The Kolmogorov-Smirnov test and histograms were used to assess the normality of numerical and continuous variables. Normally distributed numerical data were expressed as means and Standard Deviation (SD), while non-normally distributed data were presented as medians and Interquartile Range (IQR). Categorical variables were expressed as percentages (%) and counts (n). Continuous variables with normal distributions between two groups were compared using the Student's T-test, whereas the Mann-Whitney U test was employed for those not fitting a normal distribution. The Kruskal-Wallis test was used to analyze continuous variables from multiple groups without a normal distribution. Categorical variables were analyzed using Pearson's chi-square or Fisher's Exact Test. When comparing more than one group, p-values were adjusted using the Bonferroni correction. Multivariate logistic regression analysis was utilized to identify risk factors for severe illness outcomes. The significance level was set at $p < 0.050$.

RESULTS

A total of 160 patients were included in the study, with 38.8% (n=62) being female and 61.2% (n=98) male. The median age of the participants was 3 years (IQR: 1-5). Hospital admissions peaked during the spring, accounting for 34.4% (n=55) of the cases, with similar distributions across other seasons. The most commonly reported symptoms were cough (66.3%) and fever (52.5%). Upon admission, 22.5% (n=36) of the patients had low oxygen saturation. Of the patients, 41.2% (n=66) required hospitalization, with 19.6% (n=13) of these treated in the intensive care unit. Mechanical ventilation or high-flow nasal cannula (HFNC) support was necessary for 10% (n=16) of the patients: four required intubation, seven used non-invasive mechanical ventilation, and five received HFNC treatment.

The study participants were categorized into three groups based on the presence of chronic diseases. The first group, consisting of patients with primary or secondary immunodeficiencies, made up 15% (n=24) of the study population; the second group, including those with chronic lung diseases, accounted for 15.6% (n=25); the third group, comprising individuals without respiratory-affecting chronic diseases or without any chronic conditions, represented 69.4% (n=111). Lung infiltration was observed in 33.1% (n=53) of the patients. Statistical analysis showed significant associations between both chronic diseases and lung infiltration with hypoxia ($p<0.001$ for both), and with the need for mechanical ventilation ($p<0.001$ for both).

Factors influencing hypoxia included fever (OR=0.257, 95% CI 0.76-0.87, p=0.029), cough (OR= 7.66, 95% CI 1.32-44.22, p=0.023), lung infiltration (OR= 0.12, 95% CI 0.03-0.48, p=0.003), and the presence of chronic diseases (OR= 0.27, 95% CI 0.08-0.9, p=0.033).

Blood tests were conducted on 54% (n=87) of the patients, revealing leukopenia in 3% (n=5) and leukocytosis in 13% (n=22). C-reactive protein (CRP) levels were positive in 20% (n=18) and negative in 80% (n=69) of the cases. Three patients died from complications associated with HPIV; two of these had immunodeficiency, and one had chronic lung disease.

DISCUSSION

HPIV infections typically present with mild symptoms in children; however, the presence of chronic diseases can significantly increase morbidity and mortality. Our study aimed to delineate the clinical features of HPIV infections and identify factors that contribute to a poorer prognosis. The insights gained provide valuable guidance for managing and treating the disease in pediatric patients.

HPIV infections are predominantly observed in the spring and late winter seasons (8,9). Our findings align with general patterns described in the literature, where PIV-3 infections often reach epidemic levels in the summer, while other subtypes peak from autumn to spring (10). PIV-4 infections are more frequent in late summer and autumn (11,12). The reasons for these seasonal variations in subtypes are not fully understood but may relate to regional rainfall patterns, possibly influencing the genetic structure of the viruses (10). Since our study did not differentiate between subtypes, we cannot comment on specific subtype-related outcomes.

In both children and adults, chronic diseases such as immunodeficiency, chronic lung disease, and heart failure are associated with more severe HPIV infections (13,14).

Studies have reported severe pneumonia in children with severe combined immunodeficiency syndrome (SCID) and the progression from upper respiratory infections to pneumonia and respiratory failure in transplant patients (15,16). Our study corroborates these findings, demonstrating a significant association between chronic diseases and increased needs for hypoxia management and ventilatory support. It is crucial to rigorously assess children with chronic conditions, given their elevated risk for serious morbidity and mortality.

In a study on hospitalized patients diagnosed with HPIV infection, cough was the most common reason for admission, affecting 82.2% of cases (17). Another study reported that fever was the most frequent cause of emergency admissions, followed by cough (18). Swamy et al. (16) noted that cough was present in all patient admissions. These findings indicate that fever and cough are the most common symptoms. Similarly, our study found that fever and cough were the most prevalent symptoms. The variation in results across different studies may be due to the differing priorities of symptoms that prompt different populations to seek hospital care. Moreover, the absence of prominent symptoms in the early stages of infection could result in a lower reported frequency of fever.

Lower respiratory tract infections are frequently associated with HPIV infections. In a study involving 743 patients, of whom 69 were diagnosed with HPIV, the incidence of lung infiltration was reported to be 15.94% (n=11) (19). Another study observed that 9.6% (n=21) of patients exhibited lung infiltration, 7.7% (n=17) required admission to the intensive care unit, and 3.2% (n=7) needed mechanical ventilation (20). Similar rates were observed in our study. It is recommended that chest radiography be performed in selected children diagnosed with HPIV, as those showing lung infiltration on chest radiographs may require intensive care admission and respiratory support.

CONCLUSION

While HPIV infections are commonly associated with croup, they can also lead to severe lower respiratory tract infections. Hospitalized patients may necessitate intensive care and mechanical ventilation, either invasive or non-invasive. The presence of chronic diseases and lung infiltrations adversely affects patient prognosis. Therefore, careful monitoring is imperative for children with HPIV infection presenting with fever and cough, especially those with radiographic evidence of lung infiltration or a history of chronic illness, as they may develop a need for intensive care or mechanical ventilation during their illness course.

Limitations:

The main limitations of our study include its single-center, retrospective design. Factors such as access to healthcare facilities, particularly in rural areas, and delays in seeking care due to socioeconomic reasons could significantly influence the clinical course observed. Multi-center and prospective studies are essential to obtain a more comprehensive understanding of HPIV infections and their outcomes.

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Original Article

Evaluation of the Wellness of Children's and Affecting Factors during the COVID-19 Pandemic Process

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ABSTRACT

Objective: This study was carried out to assess the well-being of children and adolescents under lockdown conditions during the COVID-19 pandemic and the factors affecting it.

Material and Methods: This descriptive and cross-sectional study was conducted with 282 parents of children aged between 3-14. "Socio-Demographic Data Collection Form" and "The Well-Being of Children in Lockdown Scale (WCLS)" were used in data collection. Descriptive statistics and multiple regression analysis were used to analyze the data.

Results: The majority of participants' (97.9%, n=276) total scores on the Well-being of Children in Lockdown Scale ranged between 45 and 66, and the level of their well-being was moderate. It was found that eleven variables explained 8.7% of the variance in the total score of the Well-being of Children in Lockdown Scale (R^2=0.087, p=0.009). The variables that had a significant effect on the scores of the sub-dimensions of the scale were the age of the mother (p=0.006), the financial status of the family (p=0.004) and the number of children (p=0.010) in the physical activity sub-dimension; the status of going to school (p<0.001), financial status of family (p=0.001) and the child's age (p=0.001) in the addiction sub-dimension; the age of the mother (p=0.004), the age of the father (p<0.001) and father's employment status (p=0.003) in the emotions sub-dimension; the child's age (p=0.048), the age of the father (p=0.046) and father's employment status (p=0.010) in the fun and creative activities sub-dimension.

Conclusion: In this study, the well-being level of children and adolescents was determined to be moderate. It is recommended to plan studies on other variables that can predict children and adolescents' well-being and to make timely interventions necessary for them.

Key Words: Child, COVID-19, Health, Lockdown, Well-being

INTRODUCTION

The quarantine imposed to control the COVID-19 pandemic has greatly affected the lives of children and adolescents (1). The closure of schools, where children and adolescents spend a considerable amount of time, and the increase in time spent at home led to significant changes in their lives (1,2). Their daily routines changed drastically, and they had more free time. However, lockdowns and fear of contracting the virus forced children to spend most of their time at home (2,3). The isolation of children and adolescents in their homes adversely affected their physical, emotional, social, and academic well-being and caused significant deterioration in their quality of life (1-3). From a holistic perspective, well-being has been defined as a multidimensional structure that includes mental/psychological, physical, and social aspects (3,4). The World

Conflict of Interest : On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics Committee Approval: This study was conducted in accordance with the Helsinki Declaration Principles. Approval was obtained from Hakkari University Scientific Research and Publication Ethics Committee (Date: 09/11/2022, Decision No: 2022/96-1) for data collection.

Contribution of the Authors* : *DEMİR KÖSEM D: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***BEKTAŞ:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar.

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Health Organization defines health as a multidimensional state of physical, mental, and social well-being and draws attention to well-being (5). In fact, the concept of well-being focuses on healthy lifestyle behaviors (6-8).

The COVID-19 pandemic has caused significant deterioration in the healthy lifestyle behaviors and well-being (in terms of physical, emotional, social, and academic aspects) of children and adolescents (1,2). From a physical point of view, some studies indicated that the confinement of children and adolescents at home caused unhealthy diet, weight gain, decrease in physical activity, increase in sedentary behavior, deterioration in sleep patterns, and inadequate exposure to sunlight (9-13). In studies conducted from an emotional and psychological point of view, it was determined that lockdowns caused negative emotional states, such as fear, anxiety, and unhappiness among children and adolescents (10-12). From a social and academic perspective, children and adolescents were prevented from going to school due to lockdown and social distancing measures (2,10,11). For this reason, their social interactions were limited and they were deprived of opportunities to socialize with their peers and play games (10,11).

There are cross-sectional studies in the literature on the assessment of the physical, emotional, social, and academic well-being of children and adolescents under lockdown conditions during the COVID-19 pandemic, but there are very few studies on the evaluation of these dimensions from a holistic perspective (9,11,13).

This study was carried out to evaluate the well-being of children and adolescents under lockdown conditions during the COVID-19 pandemic and the factors affecting it and to contribute to the literature on this topic.

MATERIALS and METHODS

Study Design and Participants

A descriptive and cross-sectional study design was used. The study was carried out with parents who had children aged 3-14 years and lived in the western and eastern provinces of Turkey between November and December 2022. The sample size was calculated as 118 parents by doing a regression analysis on G*Power 3.0 statistics software, based on a Type I error of 0.05, a Type II error of 0.20 (80% power), and a medium effect size. In case the parametric test assumptions were not met, the sample size was increased by 10% and the study was planned to include 130 parents. However, all parents who voluntarily agreed to participate in the study during the data collection phase were included in the study. The convenience sample method was used to recruit samples from the research population. In the study, the data were collected online via a questionnaire created on Google Forms by sharing the link to the form on the social media of the researchers (Twitter, Facebook, Instagram, WhatsApp, or e-mail). In addition, the parents participating in the study were asked to send the link to the data collection form to their acquaintances that had children aged 3-14. The inclusion criteria of the study were volunteering to participate in the research, having Turkish reading and writing skills, and having children aged 3-14 years. In this process, the number of parents who accepted to participate in the research and completed the online questionnaire was 282. Parents were requested to complete the scale questions by considering the period of the pandemic and the effects of the children during that period. Furthermore, as the lockdown concluded during this period and the effects of the lockdown persisted, the scale was employed to ascertain the impact of events that transpired during that period on the children. Before the study was initiated, approval of the Scientific Research and Publication Ethics Committee of a university (Date: 09/11/2022, Decision No: 2022/96-1) and the permission of the owner of the scale used in the study were obtained. The study was carried out in accordance with the principles of the Declaration of Helsinki, information about the research and data collection tools was provided on the first page of the online data collection form, and consent of the parents of the children was obtained through an informed consent form.

Data Collection Tools

Demographics form was planned to be filled out by the parents. It consists of a total of 12 questions about the child's age, gender, status of going to school, mother's and father's age, education, job, and financial status, number of children, and the person filling out the questionnaire. The Well-Being of Children in Lockdown Scale (WCLS) was developed by Berasategi et al. (14) to assess the well-being of children under lockdown conditions. It consists of 22 items and all of the items are in a four-point likert type. The factor loading values ranged from 0.701 to 0.825. Cronbach's alpha was determined as 0.80 for the total scale. Scores on the scale range between 22 and 88, and as the score obtained from the scale increases, the well-being of children increases, as well. Scores are interpreted as follows: 0-22, a very low level of well-being; 23-44, a low level of well-being; 45-66, moderate well-being; 67-88, a high level of well-being (14). The Turkish validity and reliability study of the scale was performed by Demir et al. (15). Cronbach's alpha of the scale was found to be 0.89. Factor loads ranged between 0.42 and 0.95, and the scale explained 61.02% of the total variance. The scale was found to be valid and reliable for the Turkish sample (15).

Statistical Analysis

The study data were analyzed with IBM Statistical Package for the Social Sciences, version 24.0 (SPSS Inc., Armonk, NY, IBM Corp., USA). Data were evaluated using descriptive statistics (mean, standard deviation, minimum, maximum, frequency, and percentage). The normality of the data was evaluated with the Skewness-Kurtsosis tests. The predictive power of

independent variables on the mean scores of the WCLS and its sub-dimensions was evaluated with multiple regression analysis. The existence of multicollinearity was examined with Variance Inflation Factor (VIF) and tolerance values in the regression analysis. The statistical significance was taken as $p<0.050$.

RESULTS

The mean age was 37.06±5.50 years for mothers, 39.30±6.22 years for fathers, and 9.21±3.68 years for children. The mean number of children was 1.64±0.73 (min=1 and max=4), 59.9% (n=169) were girls, and 40.1% (n=113) were boys. Of the children, 46.5% (n=131) were high school students, 30.1% (n=85) were primary and secondary school students, 18.4% (n=52) were kindergarten students, and 5.0% (n=14) did not go to school. Also, 67.1% (n=189) of the mothers and 71.9% (n=203) of the fathers were university graduates, 72.3% of the mothers (n=204) and 94.3% of the fathers (n=266) had a job. Regarding the financial status, 60.6% (n=171) of the parents had equal income and expenses and 10.3% (n=29) had less income than their expenses (Table I).

When the scores of the participants on the total WCLS were evaluated, it was found that the scores of 97.9% (n=276) were between 45 and 66, 1.4% (n=4) between 67 and 88, and 0.7% (n=2) between 23 and 44. Accordingly, it was found that the well-being of children and adolescents under lockdown conditions was moderate.

The multiple regression analysis conducted to evaluate the co-effect of eleven independent variables. The result of the analysis indicated that all variables explained 8.7% of the variance in the total WCLS score (R^2=0.087, p=0.009). The decline in the child's age (β=-0.178) and status of going to school (β=-0.198) had a positive impact on the overall WCLS score (Table II). All variables explained 9.1% of the variance in the physical activity sub-dimension score (R^2=0.091, p=0.006). The results indicated that an increase in the mother's age (β=0.362) and the economic status of the family (β=0.197) had a positive effect on the physical activity sub-dimension score, while in the number of children (β=-0.178) had a negative effect (Table II). It was determined that all variables explained 18.4% of the variance in the addiction sub-dimension score of the WCLS (R^2=0.184, p<0.001). A decrease in the child's age (β=-0.263) and their status of going to school (β=-0.229) was found to have a positive effect on the addiction sub-dimension score (Table II). It was determined that all variables explained 14.8% of the variance in the emotions sub-dimension score of the WCLS (R^2=0.148, p<0.001). The increase in the mother's age (β=0.365) and the decrease in the father's age (β=-0.502) and father's employment status (β=-0.205) had a significant positive effect on the emotions sub-dimension score of the WCLS (Table II). All variables explained 11.4% of the variance in the playful and creative activities sub-dimension score (R^2=0.114, p=0.001). The decrease in the child's age (β=-0.154), the increase in the father's age (β=0.268) and father's employment status (β=0.180) had a positive effect on the playful and creative activities sub-dimension score (Table II).

Table I: Descriptive characteristics of the participants

Sociodemographic characteristics	
Children's age*	9.21±3.68 (3-14)
Mother's age	37.06±5.50 (22-61)
Father's age	39.30±6.22 (25-63)
Number of children	1.64±0.73 (1-4)
Children's gender†	
Female	169 (59.9)
Male	113 (40.1)
Children's school attendance†	
Not going to school	14 (5.0)
Pre school	52 (18.4)
Primary and middle school	85 (30.1)
High school	131 (46.5)
Mother's education level†	
Illitarete	4 (1.4)
Primary and secondary education	17 (6.1)
High school	72 (25.5)
University	189 (67.1)
Father's education level†	
Illitarete	4 (1.4)
Primary and secondary education	11 (3.9)
High school	64 (22.7)
University	203 (71.9)
Mother's employment status†	
Working	204 (72.3)
Not working	78 (27.7)
Father's employment status†	
Working	266 (94.3)
Not working	16 (5.7)
Economical situation†	
Income equals expenses	171 (60.6)
Income is higher than expenses	82 (29.1)
Income is less than expenses	29 (10.3)

***:** *mean±SD (Min-Max),* **†:** *n(%),* ***SD:** Standard Deviation,* ***Min.-Max:** Minimum and Maximum*

The evaluation of the co-effect of the eleven independent variables on the academic and routine sub-dimension scores of the WCLS with multiple regression analysis indicated that the variables of the child's age, gender, status of going to school, the number of children, parents' age, education level, employment status, and the economic status of the family did not significantly explain the scores (p=0.618 and p=0.100 respectivily) (Table II).

DISCUSSION

The results of the study demonstrated that the majority of participants exhibited moderate levels of scores on the WCLS, with a range of 45 to 66 points. High scores on the total

Table II: The effect of independent variables on the Well-Being of Children in Lockdown Scale and its sub-dimensions: results of the multiple regression analysis (n=282)

Dependent variable	Independent variables	Beta	Standard Error	β	t	p	95% Confidence interval Lower limit	Upper limit	Model statistics
WCLS (Total)	Constant	58.082	2.569		22.610	<0.001	53.024	63.140	r=0.295 r^2=0.087 F=2.348 p=0.009 DW=1.831
	Child's age	-0.169	0.075	-0.178	-2.260	0.025	-0.316	-0.022	
	Gender	0.201	0.420	0.028	0.477	0.634	-0.627	1.028	
	Status of going to school	-0.538	0.178	-0.198	-3.024	0.003	-0.888	-0.188	
	Number of children	0.350	0.323	0.074	1.083	0.280	-0.286	0.985	
	Mother's age	0.051	0.083	0.081	0.616	0.538	-0.112	0.215	
	Mother's Level of education	0.212	0.359	0.056	0.591	0.555	-0.494	0.918	
	Mother's Employment status	-0.623	0.525	-0.086	-1.187	0.236	-1.658	0.411	
	Father's age	-0.008	0.076	-0.014	-0.102	0.919	-0.157	0.142	
	Father's Level of education	-0.162	0.339	-0.041	-0.478	0.633	-0.830	0.506	
	Father's Employment status	-0.869	1.051	-0.058	-0.827	0.409	-2.938	1.200	
	Financial status of the family	0.162	0.398	0.028	0.406	0.685	-0.623	0.946	
Academic	Constant	8.763	0.765		11.456	<0.001	7.257	10.269	r=0.180 r^2=0.032 F= 0.822 p=0.618 DW=1.856
	Child's age	0.008	0.022	0.030	0.372	0.710	-0.035	0.052	
	Gender	0.067	0.125	0.032	0.532	0.595	-0.180	0.313	
	Status of going to school	0.025	0.053	0.032	0.471	0.638	-0.079	0.129	
	Number of children	-0.011	0.096	-0.008	-0.119	0.906	-0.201	0.178	
	Mother's age	-0.024	0.025	-0.128	-0.951	0.342	-0.072	0.025	
	Mother's Level of education	0.054	0.107	0.050	0.509	0.611	-0.156	0.265	
	Mother's Employment status	-0.107	0.156	-0.051	-0.683	0.495	-0.415	0.201	
	Father's age	0.010	0.023	0.063	0.449	0.654	-0.034	0.055	
	Father's Level of education	-0.051	0.101	-0.045	-0.504	0.615	-0.250	0.148	
	Father's Employment status	0.130.	0.313	0.024	0.331	0.741	-0.513	0.720	
	Financial status of the family	0.270	0.119	0.161	2.280	0.023	0.037	0.504	
Physical activity	Constant	5.937	0.528	-0.093	11.233	<0.001	4.896	6.977	r=0.301 r^2=0.091 F= 2.454 p=0.006 DW=2.081
	Child's age	-0.018	0.015	0.007	-1.185	0.237	-0.048	0.012	
	Gender	0.010	0.086	-0.090	0.117	0.907	-0.160	0.180	
	Status of going to school	-0.051	0.037	-0.178	-1.381	0.168	-0.123	0.022	
	Number of children	-0.173	0.066	0.362	-2.604	0.010	-0.304	-0.042	
	Mother's age	0.047	0.017	-0.093	2.768	0.006	0.014	0.081	
	Mother's Level of education	-0.072	0.074	-0.076	-0.979	0.329	-0.217	0.073	
	Mother's Employment status	-0.113	0.108	-0.185	-1.050	0.295	-0.326	0.099	
	Father's age	-0.021	0.016	-0.078	-1.366	0.173	-0.052	0.009	
	Father's Level of education	-0.063	0.070	0.026	-0.908	0.365	-0.201	0.074	
	Father's Employment status	0.079	0.216	0.197	0.367	0.714	-0.346	0.505	
	Financial status of the family	0.236	0.082		2.885	0.004	0.075	0.398	
Addiction	Constant	5.515	1.397		3.949	<0.001	2.765	8.265	r=0.428 r^2=0.184 F= 5.517 p<0.001 DW=1.381
	Child's age	-0.143	0.041	-0.263	-3.520	0.001	-0.223	-0.063	
	Gender	0.258	0.229	0.063	1.128	0.260	-0.192	0.708	
	Status of going to school	-0.358	0.097	-0.229	-3.698	<0.001	-0.548	-0.167	
	Number of children	0.338	0.176	0.124	1.925	0.055	-0.008	0.683	
	Mother's age	-0.020	0.045	-0.056	-0.448	0.654	-0.109	0.069	
	Level of education	0.350	0.195	0.161	1.797	0.073	-0.034	0.734	
	Employment status	-0.344	0.286	-0.083	-1.206	0.229	-0.907	0.218	
	Father's age	0.085	0.041	0.265	2.067	0.040	0.004	0.167	
	Level of education	0.005	0.185	0.002	0.025	0.980	-0.359	0.368	
	Employment status	-0.193	0.571	-0.022	-0.338	0.736	-1.318	0.932	
	Financial status of the family	-0.716	0.217	-0.214	-3.306	0.001	-1.143	-0.290	
Emotions	Constant	14.789	0.892		16.576	<0.001	13.033	16.546	r=0.384 r^2=0.148 F= 4.254
	Child's age	0.010	0.026	0.031	0.404	0.686	-0.041	0.062	
	Gender	-0.205	0.146	-0.080	-1.405	0.161	-0.493	0.082	
	Status of going to school	-0.113	0.062	-0.116	-1.827	0.069	-0.235	0.009	
	Number of children	0.214	0.112	0.126	1.908	0.057	-0.007	0.435	
	Mother's age	0.083	0.029	0.365	2.883	0.004	0.026	0.140	
	Mother's Level of education	-0.151	0.125	-0.111	-1.209	0.228	-0.396	0.095	
	Mother's Employment status	-0.055	0.182	-0.021	-0.304	0.761	-0.415	0.304	

Dependent variable	Independent variables	Beta	Standard Error	β	t	p	95% Confidence interval Lower limit	Upper limit	Model statistics
Emotions	Father's age	-0.101	0.026	-0.502	-3.825	<0.001	-0.153	-0.049	p<0.001 DW=1.577
	Father's Level of education	-0.184	0.118	-0.130	-1.565	0.119	-0.417	0.048	
	Father's Employment status	-1.110	0.365	-0.205	-3.042	0.003	-1.829	-0.392	
	Financial status of the family	0.134	0.138	0.064	0.971	0.332	-0.138	0.407	
Playful and creative activities	Constant	10.627	0.696		15.273	<0.001	9.257	11.997	r=0.337 r^2=0.114 F= 3.145 p=0.001 DW=1.858
	Child's age	-0.040	0.020	-0.154	-1.986	0.048	-0.080	0.000	
	Gender	0.012	0.114	0.006	0.110	0.913	-0.212	0.237	
	Status of going to school	-0.072	0.048	-0.097	-1.499	0.135	-0.167	0.023	
	Number of children	-0.040	0.087	-0.031	-0.459	0.647	-0.212	0.132	
	Mother's age	-0.024	0.023	-0.140	-1.085	0.279	-0.069	0.020	
	Mother's Level of education	0.002	0.097	0.002	0.020	0.984	-0.189	0.193	
	Mother's Employment status	0.228	0.142	0.115	1.599	0.111	-0.053	0.508	
	Father's age	0.041	0.021	0.268	2.003	0.046	0.001	0.082	
	Father's Level of education	0.002	0.092	0.002	0.027	0.978	-0.178	0.183	
	Father's Employment status	0.743	0.285	0.180	2.608	0.010	0.182	1.303	
	Financial status of the family	0.179	0.108	0.112	1.654	0.099	-0.034	0.391	
Routine	Constant	12.451	0.614		20.263	<0.001	11.241	13.660	r=0.247 r^2=0.061 F= 1.596 p=0.100 DW=1.638
	Child's age	0.014	0.018	0.062	0.772	0.441	-0.021	0.049	
	Gender	0.059	0.101	0.035	0.583	0.560	-0.139	0.257	
	Status of going to school	0.030	0.043	0.048	0.715	0.475	-0.053	0.114	
	Number of children	0.022	0.077	0.020	0.289	0.773	-0.130	0.174	
	Mother's age	-0.011	0.020	-0.074	-0.558	0.577	-0.050	0.028	
	Mother's Level of education	0.028	0.086	0.032	0.328	0.743	-0.141	0.197	
	Mother's Employment status	-0.231	0.126	-0.136	-1.837	0.067	-0.478	0.017	
	Father's age	-0.022	0.018	-0.168	-1.222	0.223	-0.058	0.014	
	Father's Level of education	0.130	0.081	0.140	1.597	0.112	-0.030	0.289	
	Father's Employment status	-0.490	0.251	-0.138	-1.951	0.052	-0.985	0.004	
	Financial status of the family	0.058	0.095	0.042	0.608	0.544	-0.130	0.246	

β:*Standardized Beta,* ***t:*** *t-test value,* ***R:*** *Correlation co-efficient,* ***R^2:*** *R Square,* ***F:*** *ANOVA Value,* ***DW:*** *Durbin-Watson*

WCLS indicate that the well-being of children under lockdown conditions is at a good level. In accordance with the findings of Berasategi Sancho et al. (16), the well-being of children under lockdown conditions was determined to be moderate. The result of this research is similar to that of our study.

In a study conducted in the literature, it was determined that the well-being of younger children (2-6 years old) under lockdown conditions was higher than other age groups, and that the well-being of girls was higher than boys (16). In our study, it was determined that the child's age and the child's school attendance affected the well-being of children under lockdown conditions. It has been determined that the decrease in scores in these variables has an effect on increasing the total well-being scores of children and adolescents under confinement conditions. It was found that other variables did not significantly explain the well-being of children and adolescents under lockdown conditions. This study is similar to a study in the literature, especially in terms of age group. It is thought that the reason for the different results may be due to intercultural differences (17-20).

In a study conducted in the literature, it was determined that the well-being assessment scale physical activity sub-dimension score of younger children (2-6 years old) was higher than other age groups, and the well-being assessment scale physical activity sub-dimension score of girls was higher than that of boys (16). In another study, it was found that children with poor economic conditions under lockdown conditions had a decrease in their physical activity levels and an increase in their sedentary behavior, especially that they spent more time in front of the screen (21). It has been determined that girls under lockdown conditions do less physical activity than boys, and children whose parents are working and whose parents have a high level of education do more physical activity, play games, and socialize online (21). In our study, the age of the mother and the economic status of the family positively affect the physical activity sub-dimension score of the well-being assessment scale of children and adolescents under lockdown conditions, while the number of children negatively affects the physical activity sub-dimension score of the well-being assessment scale of children and adolescents under lockdown conditions. This study is similar to a study done in the literature, especially in terms of economic situation. No study could be found in the literature explaining this relationship between the physical activity sub-dimension and the number of children and the age of the mother. The results of this study may be related to the fact that parents tend to provide better care for children as the number of children in the family decreases and the mother gains experience and expertise with age (22,23).

In a study conducted in the literature, it was determined that the addiction sub-scale score of younger children (2-6 years old) was higher than other age groups (16). In our study, the child's age and the child's school attendance negatively affect the addiction subscale score of the well-being assessment scale of children and adolescents under lockdown conditions. Additionally, the addiction sub-dimension includes questions about children's technology use and overeating. This study found that young children frequently use technology and overeat. In the literature determined that the addiction sub-dimension score of younger children (2-6 years old) under lockdown conditions was higher than that of other age groups (16). This research is similar to our study. There is no study in the literature on the comparison of the addiction sub-dimension and the child's status of going to school. Such a result in this study may be related to the use of technology and the control of children's eating by their parents or caregivers at home as the children's status of going to school (not going to school, kindergarten, primary school, middle school, and high school) decreased (19,20,24).

In a study conducted in the literature, it was determined that the emotions sub-scale score of girls was higher than that of boys (16). In our study, the mother's age positively affects the emotions sub-dimension score of the well-being assessment scale of children and adolescents under confinement conditions, while the father's job status and the father's age negatively affect the emotions sub-dimension score of the well-being assessment scale of children and adolescents under confinement conditions. No study could be found in the literature explaining this relationship between the emotions sub-dimension and the mother's age, father's job status and father's age. In this study, as the age of mothers increases, sad, tense and irritable situations increase in children and adolescents under confinement conditions. This may be due to the mother not knowing the techniques to cope with stress. The reason for this may be that the father's lack of knowledge and experience in coping with stress techniques and the father's poor work situation reflect on the family and the child (19,21,25).

In a study conducted in the literature, it was determined that the playful and creative activities subscale score of younger children (2-6 years old) was higher than other age groups (16). Oliveira et al. (21) found that children who were under lockdown conditions and whose economic situation was not good, engaged in less leisure and play activities. The findings of our study indicate that the age of the father and the father's employment status exert a positive influence on the score for the playful and creative activities sub-dimension. Conversely, the child's age exerts a negative influence on this same sub-dimension. In a study conducted in the literature, it was determined that the playful and creative activities scores of children's under lockdown conditions increased as the age of the father and the father's job status increased (16). This study is similar to our research. In the study conducted by Oliveira et al. (21) similar to our study, it was found that the father's employment status may be related with score of the playful and creative activities sub-dimension. In other words, it has been determined that when the father's employment status, – that is, the economic situation – increases, children and adolescents under lockdown conditions are more inclined towards playful and creative activities. It was determined that girls under confinement conditions were more engaged in games and social activities than boys, and children whose parents had a higher level of education did more activities with their parents (21). A review of the literature revealed no studies that have investigated the relationship between playful and creative activities and paternal age. It was established that as paternal age increases, children and adolescents in lockdown conditions can engage in more creative activities, including theatre and music, playing various games, engaging in leisure and play activities with the family. This may be attributed to the influence of paternal knowledge and experience (19,21).

In a study conducted in the literature, it was determined that the academic sub-dimension score of the well-being assessment scale was higher in children in the middle (7-9 years) and older (10-12 years) age groups who were under lockdown conditions (16). In another study, it was found that children who were under lockdown conditions, whose economic situation was not good, and whose daily routine changed, spent less time sleeping. Again, in this study, it was determined that children whose parents had a higher education level slept more than children whose parents had a lower education level (21). In our study, when the effect of children and adolescents under lockdown conditions on the academic and routine sub-dimensions scores of the well-being assessment scale was evaluated, it was determined that the variables did not explain it significantly. In our study and other similar investigations, the factors that influence the well-being of children and adolescents in isolation conditions vary, and some factors are either absent or have no effect. The differing isolation regulations (either full or partial) and varying cultural norms across countries may contribute to this variability (17-20). More research into this subject is needed to reveal the factors affecting physical activity, addiction, emotions, playful and creative activities, academic, and routine sub-dimensions and the well-being of children and adolescents.

CONCLUSION

It was determined that the well-being of children and adolescents under lockdown conditions was moderate. The variables that had a significant effect on the physical activity, addiction, emotions, and playful and creative activities sub-dimension scores of the WCLS were determined as the child's age, status of going to school, the number of children, the mother's age, the father's age, the father's employment status, and the financial status of the family. The COVID-19 pandemic has affected children, who are in a very critical developmental period, in many ways and seems to continue to affect them in

the following periods. Pediatric nurses have a critical importance in detecting the physical, emotional, social and cognitive effects that may occur in children during this process at an early stage and in meeting the care needs of this sensitive group. Pediatric nurses should continue to use their consultancy role effectively during the pandemic process, provide the necessary information to the child and their family, and take more initiatives to improve and protect children's health by being aware of the effects of the pandemic. For this reason, it is recommended to carry out studies with larger samples to reveal the correlation between research variables more clearly and to carry out the necessary interventions and education programs, that is, the relevant support structures that may be needed after the quarantine is lifted, for children and adolescents promptly, by considering how children and adolescents cope with the pandemic. In addition, it is recommended to prepare interventions to protect children's well-being in the home environment and to evaluate applications and activities for future pandemics.

Limitations of the Research

This study has certain limitations. The first limitation may be that the questionnaire is filled only by the parents and the questions are filled in biased and properly. The use of convenience sampling is another limitation. This may affect the generalizability of the research results.

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Original Article

Body Weight Parameters at the Initial Visit for Eating Disorders in Adolescents: Are These the Markers of Serious Complications?

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ABSTRACT

Objective: Eating disorders (ED) are psychiatric disorders often accompanied by medical complications. This study aimed to identify the complications in ED patients during hospital admission and their relationship with body weight (BW).

Material and Methods: Patients diagnosed with ED per DSM-5 criteria seen at least once in the adolescent department were included. Digital medical records were used to obtain patient information. Body mass index (BMI), BMI percentile, and percentage of BW by height (IBW%) were calculated to analyze their association with medical complications.

Results: Our study included 144 patients, 140 (97.2%) females and 4 (2.8%) males. Of the patients; 94 were analysed as Anorexia Nervosa (AN), 28 as Atypical AN and 17 as Bulimia Nervosa (BN). At least one cardiac complication was detected in 29.3% (39), gastrointestinal complications in 54.2% (78), hypoglycaemia in 18.2% (26), secondary amenorrhoea in 34.5% (48) and 45.8% (66) received inpatient treatment. Patients with IBW%<75 exhibited significantly higher rates of hypoglycemia, bradycardia, low sT3, amenorrhea, and hospitalization compared to those with IBW% ≥ 75 ($p<0.001$). Bone mineral density (BMD) was significantly inversely associated with Z-score, time to ED diagnosis and duration of amenorrhoea ($p=0.006$; $p=0.044$; $p=0.032$, respectively).

Conclusion: Our findings show that at least one medical complication frequently develops in ED patients at the initial evaluation. Patients with AN and BN, which usually start in adolescence, may frequently present to paediatric outpatient clinics with medical complaints. The role of internal physicians in the early diagnosis of ED is important to prevent serious complications in these patients.

Key Words: Adolescent, Anorexia nervosa, Bulimia nervosa, Eating disorder, Medical complication

INTRODUCTION

Anorexia nervosa (AN) and bulimia nervosa (BN) are types of ED that often onset in adolescence and progress with significant complications involving all body systems (1). According to DSM-5 diagnostic criteria, lifetime AN was reported by 0.8-6.3%, BN by 0.8-2.6%, and binge eating disorder (BED) by 0.6-6.1% of young women. Avoidant/Restrictive Food Intake Disorder (ARFID) is the new definition in DSM-5 of the type formerly called "Feeding Disorder in Infancy or Early Childhood". Its incidence in children and adults varies between 0.5%-5% (2). AN is the most common cause of death among psychiatric disorders. Although some of the deaths are suicides, half of them are caused by medical complications (3).

Although the body weight (BW) of AN patients is very low compared to their peers, they are constantly preoccupied with the thought and behavior of losing weight. AN patients are dissatisfied with their weight and/or their body, sometimes

Conflict of Interest: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics Committee Approval: This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Bilkent City Hospital, Ethics Committee (23.11.2022-2860).

Contribution of the Authors: ***ÇÖLLÜ YA:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. ***TAŞ D:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***ÖDEM AKMAN A:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions. ***ÇÖP E:*** Planning methodology to reach the conclusions, Reviewing the article before submission scientifically besides spelling and grammar.

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part of their body. They usually have a restricted diet, some of them also have a one-way diet. BN and AN binge-purge subtype engage in compensatory behaviors such as vomiting and excessive exercise after consuming inappropriate food (4). Inappropriate restricted feeding, compensatory behaviors and rapid weight loss can lead to serious morbidity. Electrolyte disturbances, metabolic disorders, bradycardia and other cardiovascular pathologies are serious acute complications that should be closely monitored in patients with eating disorders (5). Common endocrine complications in patients with AN include amenorrhoea, oligomenorrhea, cessation of puberty, hypothyroidism, and hypercortisolism. In patients with amenorrhoea, osteopenia and osteoporosis are long-term complications leading to clinically significant fractures and increased risk of fractures throughout life (6).

In a review, it was stated that the degree of low BW or rapid loss of BW predicts medical complications (7). Although ED is a psychiatric disorder, patients often present to health centers due to medical complications. Adolescents with EDs may present to the pediatrician with symptoms related to weight loss, malnutrition or vomiting behaviors. Symptoms such as constipation, early feeling of satiety, oesophagitis due to vomiting may be the first reason for presentation (8). They may also present with common symptoms such as fatigue, hair loss, chills and menstrual irregularities. Life-threatening complications such as bradycardia, hypotension and hypoglycemia may be detected on examination (9).

Patients with AN and BN with onset in adolescence are more likely to present to the pediatric outpatient clinic with one of the above symptoms. Recognising and early management of medical complications accompanying eating disorders is critical for the treatment and recovery of EDs (10). This study aimed to determine the complications in eating disorder patients at first presentation and how they were related to BW.

MATERIAL and METHODS

Between April 2019 and January 2023, 144 adolescents aged 12-18 years who were diagnosed with eating disorders (AN, BN and ARFID) according to DSM-5, and admitted to Adolescent Health Department of Ankara Bilkent City Children's Hospital were included. The study was approved by Ankara Bilkent City Hospital, Ethics Committee (23.11.2022-2860). In this retrospective cross-sectional study, the symptoms and findings of the patients at the time of admission were taken from the medical records. A digital patient file containing detailed information of all systemic examination findings, water consumption and systemic symptoms such as constipation, vomiting and bowel movements characteristics was examined. Constipation was determined by using Rome-III criteria (11).

Some medical complications were evaluated in relation to BW at the time of diagnosis; BMI (weight (kg)/height^2 (m^2)); BMI-percentile, percentage of ideal body weight (%IBW) (weight (kg)/weight-for-height in the 50% percentile (kg)x100) (12).

Orthostatic blood pressure, pulse rate and body temperature (°C) were evaluated. A peak heart rate <60 beats/sec was considered bradycardia (13).

Patients' daily water intake was assessed according to the Turkey 2015 Dietary Guidelines (14). Urine density between 1007 and 1030 was considered normal. Leukocyturia was considered as 5 leukocytes per Hpf (high power field) (X40) and more in complete urine examination.

Patients who did not menstruate between 21-45 days despite 2 years after menarche, whose menstruation period lasted less than 3 days and more than 10 days, and whose daily number of pads was less than 1-2 and more than 7 were considered as irregular menstruation. Those who did not menstruate for at least 3 consecutive cycles were considered as secondary amenorrhoea (15).

Electrocardiography (ECG) was performed and pulse rate and QTc values were calculated. Echocardiographic findings (mitral valve prolapse (MVP), mitral regurgitation (MR), pericardial effusion were obtained from echocardiography and cardiological evaluation. The results of the lumbar spine BMD measurements were assessed. Normal values of complete blood count were considered according to the guidelines of the Turkish Society of Haematology for the diagnosis and treatment of erythrocyte diseases and hemoglobin disorders (16).

According to the 2022 guidelines of the International Pediatric and Adolescent Diabetes Association, blood sugar levels below 70 mg/dL are considered hypoglycemia (17).

Other disease-specific biochemistry and hormone results were evaluated on the basis of the hospital laboratory references according to the age of the patients.

Statistical Analysis

The IBM Statistical Package for Social Sciences (SPSS), Windows version 23.0 (SPSS Inc. Chicago, USA) was used for the statistical analysis of the research data. In the descriptive statistics section, categorical variables were presented as numbers and percentages; continuous variables were presented as mean ± standard deviation and median (minimum-maximum value). The conformity of continuous variables to normal distribution was assessed using visual (histogram and probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests).

As a result of the normality analyses, the paired sample t-test was used for comparison analyses between two dependent groups for data of continuous variables that were found to be normally distributed between groups.

For comparison analyses of categorical variables between independent groups, the Pearson chi-square test, continuity correction test and Fisher's exact test were used.

The relationship between BMD values and independent predictors was assessed using Pearson correlation analysis for normally

distributed data and Spearman correlation analysis for non-normally distributed data. When the absolute value of the correlation coefficient (rho) is r≤0.30, there is a weak relationship, 0.30-0.50 is a moderate relationship, and r ≥0.50 is a strong relationship. In this study, the level of statistical significance was accepted as p<0.050.

RESULTS

A total of 144 patients were included in our study, of whom 4 (2.8%) were male and 140 (97.2%) were female. Patient diagnoses were as follows: 65.3% (94) AN (restrictive and binge types), 19.4% (28) atypical AN, 11.8% (17) BN and 3.5% (5) ARFID. Hospitalisation was an indication in 45.8% (66) of the patients.

Of the hospitalised patients, 80.3% (53) were diagnosed with AN, 9.1% (6) with atypical AN, 9.1% (6) with BN and one patient with ARFID.

At admission, 81.9% (118) of the patients had lost weight, 13.9% (20) had vomited, 3.5% (5) had lost their appetite, and 0.7% (1) had binge eating. The mean age at presentation was 14.96±1.52 (11.0-18.0) years. The mean difference between age at presentation and age at diagnosis was 11.75±9.18 (6.0-48.0) months. The mean BW and IBW at presentation were 47.2±9.4 (28.0-82.0) and 88.4±17.3% (56.0-150.0), respectively. Details of the patients' height, BMI, BMI(p), blood pressure (BP), pulse parameters are shown in Table I.

Orthostatic pulse difference was found in 6.1% (8) of patients, orthostatic systolic blood pressure difference in 3.8% (5) and orthostatic diastolic blood pressure difference in 9.2% (12).

Secondary amenorrhoea was found in 34.5% (48) and primary amenorrhoea in 2.9% (4) of the 139 patients whose menstruation was evaluated. Irregular menstruation was found in 38.8% (33) of the patients. The mean duration of amenorrhoea was 7.9±3.4 (4.0-18.0) months.

Of the four patients with primary amenorrhoea, three were AN restrictive and one was ARFID. Of the 48 patients with secondary amenorrhoea, 40 were AN (restrictive), two were AN (restrictive and binge type), two were BN and four were AN (atypical). The mean value of BMD Z score was -0.88±1.31.

Table I: Height and Body Weight Characteristics of the Patients at Admission

Parameters	(n=144)
Body Weight, kg*	47.2 (28.0-82.0)
Height, cm†	161.2±6.9
BMI, kg/m²*	18.1 (12.78-31.63)
BMI-Percentile*	20.1 (0.02-99.8)
IBW %*	88.4 (56.0-150.0)
Body Temperature °C†	36.46±0.21
Pulse (n=133)*	80.7 (45.0-120.0)
Systolic Blood Pressure, mmHg*	101.6 (80.0-130.0)
Diastolic Blood Pressure, mmHg*	65.7 (40.0-90.0)

**: median (min-max), †: mean±SD*

It was found that 47.2% (67) of the patients had dry skin, 43% (61) had hair loss and 33.8% (48) had lanugo hair growth. A total of 45 patients (31.3%) consumed less than one litre of water per day.

In total, 29.3% (39) of patients presented with at least one cardiac complication. Bradycardia was found in 23.1% (30), mitral regurgitation in 21.1% (15), pericardial effusion in 8.5% (6) and MVP in 7% (5) of all patients. The mean heart rate was 69.2±14.5 (41.0-124.0)/min and the mean corrected QT interval (QTc) was 0.39±0.05 (0-0.44)ms. None of the patients had a pathologically long QTc interval.

Of the participants, 54.2% (78) had at least one gastrointestinal complication. Vomiting was observed in 29.9% (43) and constipation

Table II: Laboratory Parameters of Patients

Parametreler	n (%)
Creatinin, mg/dL (n=144)	
Low	4 (2.8)
High	16 (11.1)
Ure, mg/dL (n=140)	
Low	1 (0.7)
High	10 (7.1)
Uric Acid, mg/dL (n=140)	
Low	1 (0.7)
High	29 (20.7)
Total Protein, g/L (n=139)	
Low	15 (10.8)
High	1 (0.7)
Albumin, g/dL (n=141)	
Low	2 (1.4)
High	56 (39.7)
Aspartate aminotransferase (AST), U/L (n=143)	
High	16 (11.2)
Alanine aminotransferase (ALT), U/L (n=139)	
High	18 (12.9)
TSH, mU/L (n=139)	
Low	4 (2.9)
High	2 (1.4)
rT4, ng/dl (n=139)	
Low	5 (3.6)
High	4 (2.9)
rT3, ng/L (n=102)	
Low	65 (62.5)
High	1 (1.0)
Leucocyte, x 10^9/L (n=144)	
Low	23 (16.0)
High	2 (1.4)
Hemoglobin, g/dL (n=144)	
Low	13 (9.0)
High	5 (3.5)
Neutrophile, x 10^9/L (n=144)	
Low	16 (11.1)
High	1 (0.7)
Trombocyte, x 10^9/L (n=141)	
Low	4 (2.8)
High	2 (1.4)

Table III: Body Weight parameters according to the presence of hypoglycaemia and bradycardia in patients

	Hypoglycemia			Bradycardia		
	Yes n=26 (%)	**No n=117(%)**	**p**	**Yes n=30 (%)**	**No n=100 (%)**	**p**
BMI, kg/m^2						
≥18	6 (9.1)	60 (90.9)	0.017*	9 (15.3)	50 (84.7)	0.085*
<18	20 (26.0)	57 (74.0)		21 (29.6)	50 (70.4)	
BMI-p						
≥5	10 (13.2)	66 (86.8)	0.149*	10 (15.2)	56 (84.8)	0.049*
<5	16 (23.9)	51 (76.1)		20 (31.2)	44 (68.8)	
IBW						
≥ %75	14 (13.1)	93 (86.9)	0.008*	15 (16.0)	79 (84.0)	0.006*
< %75	12 (35.3)	22 (64.7)		14 (41.2)	20 (58.8)	

***:** *Continuity Correction test*

Tablo IV: BMI, BMI-p and IBW % according to the presence of amenorrhea and sT3 levels in patients

Parameters	**Amenorrhea (Primer and Seconder)**			**sT3**		
	Yes n=52 (%)	**No n=87 (%)**	**p**	**Normal n=38 (%)**	**Low n=65 (%)**	**p**
BMI, kg/m^2						
≥18	11 (21.2)	55 (63.2)	<0.001*	29 (65.9)	15 (34.1)	<0.001*
<18	41 (78.8)	32 (36.8)		9 (15.3)	50 (84.7)	
BMI-p						
≥5	17 (32.7)	59 (67.8)	<0.001†	28 (54.9)	23 (45.1)	<0.001*
<5	35 (67.3)	28 (32.2)		10 (19.2)	42 (80.8)	
IBW						
≥%75	29 (55.8)	77 (88.5)	<0.001†	36 (49.3)	37 (50.7)	<0.001*
< %75	23 (44.2)	10 (11.5)		2 (7.1)	26 (92.9)	

***:** *Pearson Chi-kare test,* **†:** *Continuity Correction test*

in 51.4% (74) of the patients. Three patients had oesophagitis, two had rectal bleeding and one had hemorrhoids. At least one endocrinological complication was found with 68.1% (98) of the patients. Hypoglycemia occurred in 18.2% (26) of the patients and the mean glucose level was 79.06±13.95 (47.0-152.0) mg/dl.

The creatinine level was found to be high in 11.1% (16), the urea level in 7.1% (10) and the uric acid level in 20.7% (29) of the patients. Albumin level was found to be low in 1.4% (2) and high in 39.7% (56) of patients (Table II).

In our study, AST levels were found to be high in 11.2% (16) and ALT levels were found to be high in 12.9% (18) of patients. White blood cell count was low in 16% (23), hemoglobin was low in 9% (13), high in 3.5% (5) and neutrophil count was low in 11.1% (16) of the patients. Among the patients' thyroid function tests, TSH levels were low in 2.9% (4) and high in 1.4% (2); sT4 levels were low in 3.6% (5) and high in 2.9% (4); sT3 levels were low in 62.5% (62) and high in 1% (1) (Table II).

When the electrolytes of the patients were evaluated: Serum chlorine level was low in 2.9% (4) and high in 8.8% (12), potassium level was low in 4.3% (6), calcium level was low in 5.7% (8) and high in 12.9% (18), phosphorus level was low in 3.6% (5) and magnesium level was normal in all patients.

It was found that 31.3% (44) of all participants drank less water and the mean urine density was 1017.3±9.54 (1000-1042). Urine density was low in 15.6% (22), high in 7% (10) and 77.3% (109) normal range of these patients. Sterile pyuria was found in 31.4% (44) of the patients.

Thirty three (41.3%) of patients with restrictive type AN drank less water, and urine density was low in 18.7% (15) and high in 10% (10) of these patients.

The rate of sterile pyuria was not significantly higher in patients with BMI <18, BMI-p<5 and IBW <75% (p=0.227; p=0.999; p=0.221, respectively).

A statistically significant increase in the incidence of hypoglycaemia was observed in patients with a BMI of less than 18 and an IBW of less than 75% (p=0.049; p=0.006, respectively). Bradycardia was statistically significantly more common in patients with BMI-p<5 and IBW <75% and (p=0.049; p=0.006, respectively) (Table III).

Patients with BMI<18, BMI-p<5 and IBW≥75% had statistically significantly more amenorrhoea (p<0.001). The statistical analysis yielded significant results, indicating a higher prevalence of low sT3 levels among patients with a BMI less than 18, a BMI-p less than 5, and an IBW less than 75% (p<0.001) (Table IV).

There was a statistically significant higher number of hospitalisations in patients with BMI <18, BMI-p <5 and IBW <75% (p<0.001; p<0.001; p=0.015, respectively). (Table V).

The relationship between urea, creatinine and uric acid levels and body weight parameters was evaluated using Fisher's exact test. In patients with BMI <18, BMI-p<5 and IBW<75%, no significant

Table V: Body Weight parameters according to patients' hospitalisation status

Parameters	Hospitilazition		
	Yes n=66 (%)	No n=78 (%)	p
BMI, kg/m^2			
≥18	17 (25.4)	50 (74.6)	<0.001*
<18	49 (63.6)	28 (36.4)	
BMI-p			
≥5	24 (31.2)	53 (68.8)	<0.001*
<5	42 (62.7)	25 (37.3)	
IBW			
≥ %75	42 (38.9)	66 (61.1)	0.015†
< %75	22 (64.7)	12 (35.3)	

***:** *Pearson Chi-kare test,* **†:** *Continuity Correction test*

Table VI: Relationship between mean BMD Z-score and BW

	r	p
BMD Z score*Age of diagnosis	-0.401†	0.006
BMD Z score*IBW %	0.302‡	0.044
BMD Z score* BMI	0.054‡	0.726
BMD Z score*BMI-Percentil	0.183‡	0.228
BMD Z score*Amenorrhea Time	-0.363‡	0.032

***BMD:** Bone Mineral Dansity,* **r:** *Correlation coefficient,* **†:** *Pearson correlation* **‡:** *Spearman's correlation*

increases or decreases in creatinine, urea and uric acid levels were observed (for urea, p=0.751; p=0.999; p=0.451, for creatinine, p=0.301; p=0.274; p=0.535, for uric acid, p=137; p=498; p=0.511, respectively).

A significant negative correlation was found between BMD Z-score values and time to disease diagnosis (p<0.006). A moderately significant relationship was found between BMD Z score values and IBW% (p<0.044). A significant negative correlation was found between BMD values and duration of amenorrhoea (p<0.032) (Table VI).

DISCUSSION

This study investigated the relationship between the presenting signs, symptoms and complications of ED patients and their BW at the time of presentation. A total of 144 patients, of whom 4 (2.8%) male and 140 (97.2%) female were included in our study. Among the male patients, three patients were identified as AN (restrictive) type and one patient was identified as ARFID.

Anorexia nervosa represented the majority of patients followed in adolescence. This, predictably, was due to a high rate of weight loss and associated medical complications in patients with AN. The mean age at diagnosis was 14.6 years and was similar in boys and girls; however, we could not compare the ages at diagnosis because the number of male patients was very small. The peak age for ED diagnosis was 15 years for girls and 16 years for boys in a study conducted in the UK (18).

In our study, the mean difference between the ages of diagnosis and first symptoms was 11.75 months. In another study, the difference between the onset of symptoms and admission to the clinic was 11 months (19). In a long-term study, 48% of adolescents with AN were found to have growth curve abnormalities on average 9.7 months before the onset of AN-related symptoms on retrospective observation (20). These studies show that there is a delay in diagnosis in patients with AN, resulting in serious long-term morbidity. These data suggest that there may be some reasons why patients with ED are diagnosed with an average delay of 1 year. Due to the distorted body image of ED patients, they do not see themselves as sick. Diagnosis may be delayed because it takes time for parents to notice the changed eating behaviour and for medical signs to appear. As with other chronic diseases, one of these reasons may be that their access to health centers was disrupted during the Covid-19 pandemic (21).

It was observed that about half of our patients were hospitalized and the majority of the hospitalized patients were AN patients. This is because, as expected, more medical complications developed with increased BW loss. One study reported that 55% of patients with AN had at least one hospital admission (19).

In our study, significantly more hypoglycaemia was observed in patients with low BW. This finding suggests that we should be more cautious about hypoglycemia in patients with low BW because of the decrease in glycogen stores due to weight loss. A published case study reported that clinically severe hypoglycaemia may be a fatal complication of AN, although it is not very common (22). We found hypoglycaemia in 18.2% of our patients.

Elevated blood creatinine levels were found in 11.1%, urea in 7.1% and uric acid in 20.7% of our patients. In patients with anorexia nervosa, urea and creatinine levels are expected to be low due to malnutrition and low muscle tissue. However, elevated levels are a sign of severe kidney damage or dehydration. Impaired renal function was found to be more predictive of disease severity than low BMI in eating disorder patients (23).

Although the mechanism is not well understood, studies have shown that albumin levels are normal in patients with eating disorders. It has been suggested that this may be due to increased albumin transfer from the extravascular to the intravascular space by adaptive mechanisms (24). Mehler et al. (25) explain that one reason for the preservation of serum albumin levels in patients with anorexia nervosa is the absence of inflammation in these patients, and that it is not a good marker in the follow-up of patients. In our study, 39.7% of patients had a mildly elevated albumin level.

Liver transaminase levels have been found to be elevated in approximately 10% of patients, and all of these patients had a diagnosis of restrictive AN. One study showed that BMI and transaminase elevation were inversely proportional in AN patients (26).

Iron deficiency anemia is not expected in patients with AN. The main cause of anemia and other blood cell deficiencies in patients with AN is bone marrow suppression. However, abnormalities in the complete blood count are common. In our study, 16% of patients had a low white blood cell count and 11.1% had

neutropenia. Hemoglobin was found to be low in 9% of patients. As expected, iron deficiency anemia was not found. A review reported that the rate of anemia was 21-39%, leucopenia 29-39% and thrombocytopenia 5-11% (27). In a study of 60 adolescent girls diagnosed with AN, the rate of neutropenia and anemia was 22% (28). Compared to the literature, blood cell disorders were detected less frequently in our patients.

Although 41% of adolescents with AN drank less water, only 7% were found to have increased urine density. It is well known that osmoregulation is impaired in patients with AN (29). Sterile pyuria was found in 31.4% of patients.

Three of the 6 patients with hypokalemia on admission were diagnosed with AN, two with atypical AN and one with BN. Four of the five patients with hypophosphatemia were diagnosed with AN and one with atypical AN. Electrolyte imbalances are a serious complication of eating disorders. One study drew attention to this issue and recommended caution regarding undiagnosed eating disorders in patients presenting to a health center with electrolyte imbalances (30).

Secondary amenorrhoea and irregular menstruation were observed in approximately one third and one quarter of our patients, respectively. It is well known that low BW is associated with amenorrhoea, which is one of the most common complications in ED patients (31). In a study of 251 ED patients, the incidence of amenorrhoea was found to be 61% in AN patients and 11% in BN patients, and the same study found that the frequency and duration of amenorrhoea were associated with BMI. The same study reported that amenorrhoea developed in 82% of those with a BMI below 18 who exercised (32).

Cardiac complications are the most common cause of sudden death in patients with AN. Numerous cardiac abnormalities have been described in the literature, including pericardial and valvular pathologies, changes in left ventricular muscle and function, conduction abnormalities, bradycardia, hypotension, and peripheral vascular contractility abnormalities. At least one cardiac complication was observed in 29.3% of our patients. The most common cardiac complication was bradycardia and mitral regurgitation was observed with the second frequency. Sinus bradycardia is the most common cardiovascular complication in patients with AN. Bradycardia improves with nutrition and weight gain. We found that BW was inversely associated with the occurrence of bradycardia in our patients. Pericardial effusion and MVP were less common. QTc prolongation was not observed in any of our patients. Although some studies have shown QTc prolongation, most studies have reported no QTc prolongation (33).

At least one GIS complication was observed in 54.2% of patients. The most common objective GIS finding was constipation. Endoscopic oesophagitis was also found in three patients, rectal bleeding in two patients and hemorrhoids in one patient. One study reported that constipation was found in 35% of patients diagnosed with AN and in 15% of patients diagnosed with BN (34). Constipation may be expected in patients with AN in association with food and fluid restriction. However, impaired gastrointestinal motility in patients with AN and altered gut microbiota in relation to their food preferences increase the susceptibility to constipation (35).

At least one endocrine complication was observed in 68.1% of patients, the most common being hypothyroidism and menstrual disorders. In our study, sT3 levels were found to be low in 62.5% of patients. In our study, low sT3 levels were found to be significantly higher in patients with low BMI and IBW%. One study reported that the amount and rate of weight loss affected low sT3 concentrations. In addition, it was reported that low sT3 was an important determinant of weight loss in the premenopausal period, whereas low sT3 could not predict weight loss in the postmenopausal period. In the same study, serum TSH concentrations were found to be within normal limits in ED patients and were not affected by changes in BW. It was found that blood sT3 levels also increased with increasing BW and reached normal levels (36).

As seen in our study, amenorrhoea has a negative effect on bone mineral density. This increases the risk of osteopenia and osteoporosis in the long term. The severity of long-term complications also increases with the duration of the disease and its early onset. A study comparing spinal bone densities in adolescent females found that prolonged amenorrhoea was associated with decreased BMD Z-scores (37). The data from our study support this finding. A significant, negative and moderate correlation was found between BMD Z score values and age at diagnosis.

In conclusion, according to our data, medical complications affecting all body systems are common in patients with AN and BN. Although Eating Disorders are psychiatric disorders, somatic symptoms or medical complications are likely to be the reason for patients to consult a health center. Early identification of patients with weight loss or compensatory behaviors secondary to ED may prevent morbidity and mortality. Recognising possible symptoms and signs of AN and BN, which often begin in adolescence, in pediatric outpatient clinics will protect against acute and chronic complications and prevent delayed multidisciplinary treatment.

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Original Article

Acute Pancreatitis in Children: Neither to be Underestimated Nor to be Overlooked

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ABSTRACT

Objective: Despite varying presentations of acute pancreatitis (AP) in children, the diagnosis has been increasing in recent years due to increased awareness. We aimed to identify the relationship among etiology, presentation symptoms, treatment response and complications of the children with acute pancreatitis.

Material and Methods: Thirty children diagnosed with AP were evaluated for clinical and laboratory findings, treatment approaches, complications in the tertiary children hospital retrospectively.

Results: The mean age of the patients was 12.4 ± 4.3 years and 60% were male. The drugs (30%), biliary tract diseases (26.7%), infections (16.7%), hyperlipidemia (10%) were the main causes of AP, in 10% of patients no etiological factor was detected. Abdominal pain (83.3%), nausea (70%), loss of appetite (63.3%), vomiting (56.7%), and fever (20%) were the most common symptoms. Ultrasonography, abdominal tomography and magnetic resonance cholangiopancreatography revealed pancreatitis related changes 63.3%, 85%, 70% of patients, respectively. Oral feeding was started on median 4 days (1-30), with polymeric diet (30%), and medium chain triglyceride rich enteral diet (70%). The median length of hospitalization (LOH) was 16.5 days (4-66). The patients fed with polymeric diet had a shorter hospitalization duration ($p<0.036$). The delayed initiation of oral feeding caused longer LOH ($p<0.001$).

Conclusion: Consequently, this study underlines the children with acute abdominal pain, especially who use drugs like asparaginase and valproic acid, or that are known to have gallstone/biliary sludge, need to be examined for acute pancreatitis through pancreatic enzymes and ultrasonography. Moreover, the study also highlights that early feeding in acute pancreatitis is related with shorter hospitalization duration.

Key Words: Acute Pancreatitis, Children, Etiology, Treatment

INTRODUCTION

Inflammation of pancreas is defined as acute pancreatitis (AP). Acute pancreatitis generally presents with an abrupt stomachache. The pancreas enzymes are elevated, and specific findings are detected in imaging studies (1-2). The most frequently observed causes of AP in children are biliary and systemic diseases, drugs, and trauma (2-6). Despite the disease's typically mild course in children, severe, systemic involvement and even death are also reported. The primary symptom is abdominal pain, occurring in 80-95% of cases. In younger children, irritability may also be observed (2,7,8). Nausea and vomiting are the second leading symptoms, occurring with or without severe abdominal pain. The diagnosis of AP has increased among children due to the increase in awareness (3-6). However, despite increased diagnostic capacity, lack of knowledge about the epidemiology, most common underlying causes, established diagnostic criteria, imaging techniques, appropriate management strategies and complications of AP persists. This lack of knowledge often leads to delay in diagnosing and treating AP (7, 9,10).

There are few publications focusing on AP in children. We aimed to examine the demographic and clinical characteristics, laboratory

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Ethics Committee Approval : This study was conducted in accordance with the Helsinki Declaration Principles. Approval for the study was received from the education board of Ankara Child Health and Diseases Training and Research Hospital (08/06/2012-126).

Contribution of the Authors* : *CURA YAYLA BC: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study. ***TUNA KIRSAÇLIOĞLU C:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Reviewing the article before submission scientifically besides spelling and grammar. ***ŞAYLI TR:*** Organizing, supervising the course of progress and taking the responsibility of the research/study , Reviewing the article before submission scientifically besides spelling and grammar.

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and imaging findings, treatment modalities, complications, mortality, and morbidity rates of pediatric patients with acute AP who treated in our center.

MATERIALS and METHODS

A comprehensive retrospective examination was conducted on the medical files pertaining to the pediatric AP cases in University of Health Science Ankara Training and Research Hospital. This entailed a thorough analysis of the initial admission reports of clinical, laboratory, and imaging tests, as well as the treatment administered. The results were recorded in a dedicated form, based on the data extracted from the patient files. The diagnosis of the patients was made by the researchers who primarily conducted the study.

According to INSPPIRE (11), the International Study Group of Pediatric Pancreatitis: In Search for a Cure, diagnosing acute pancreatitis (AP) in children involves meeting at least two of the following three criteria:

1. Typical abdominal pain,
2. Serum amylase and/or lipase levels at least three times the upper limit of normal (ULN)
3. Imaging studies showing characteristic findings of AP.

Patients with recurrent attacks of acute pancreatitis and chronic pancreatitis were excluded. Approval for the study was received from the education board of Ankara Child Health and Diseases Training and Research Hospital (08/06/2012-126).

The demographic and clinical features, treatment procedure, complications, length of hospitalization (LOH), morbidity and mortality rates were recorded. Additionally, complete blood count (CBC), biochemical parameters including serum electrolytes, hepatic enzymes, renal function tests, lipid profile, serum amylase, lipase, pancreatic amylase, acute phase reactants (like C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)), prothrombin time, partial thromboplastin time were recorded according to age (12). Furthermore, specific investigations for the etiology, imaging procedures including ultrasonography (USG), computed tomography (CT) and magnetic resonance cholangiopancreatography (MRCP) were also evaluated.

The LOH was compared with the type of oral nutrition (polymeric diet or medium chain triglyceride (MCT) and whether the patient received total parenteral nutrition (TPN)).

Patients' anthropometric measurements were recorded at initial date of hospitalization. A patient was classified as having short stature if the height-for-age z-score was below -2. A patient was classified as underweight if the weight-for-age z-score was less than -2. The classification of body mass index (BMI) percentiles according to sex and age is as follows: underweight is defined as a BMI below 5%, overweight as a BMI between 85% and 95%, and obesity as a BMI above 95% (13).

If no etiological cause could be identified based on history, laboratory tests, and imaging methods, these patients were classified as "idiopathic AP". The following conditions were included as the category of "biliary disease related AP": gallstones, biliary sludge, annular pancreas, choledochal cyst, and other biliary tract disorders. Acute pancreatitis in patients who had used drugs, and if the condition resolved when the drugs were discontinued was defined as "Drug-related pancreatitis" (7).

For the statistical analysis, patients were separated into two groups (mild or severe AP), based on the criteria outlined by Atlanta, DeBanto, Acute Physiology and Chronic Health Evaluation II, Ranson, and Modified Glasgow. In recent years the Pancreas Committee of the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) criteria was used to further classify acute pancreatitis as mild, moderately severe, or severe acute pancreatitis (4,14-18).

IBM Statistical Package for the Social Sciences, version 21.0 (SPSS Inc., Armonk, NY, IBM Corp., USA) was used for the statistical analysis. The Kolmogorov-Smirnov test was utilized to determine the conformity of variables to a normal distribution. Continuous variables were analyzed using the mean, standard deviation or median (minimum-maximum) and categorical variables using frequency and percentage for descriptive statistics. The student's t-test was used to assess the significance of differences between groups in terms of mean values, while the Mann-Whitney U test for the differences between median values. The Chi-Square test was performed for the analysis of categorical variables. $p<0.050$ was accepted as statistically significant.

RESULTS

There were 30 children with a diagnosis of AP, male patients consisted of 60% (n=18). The mean age of these patients was 12.4 ± 4.3 years, with a range of 3 to 18 years. Comparison of gender of patients due to mean age did not show any significance [girls 11.1±4.9 years (range: 3-17 years), boys 13.3±3.8 years (range: 6-18 years), p=0.176].

The most common presenting symptom was abdominal pain at the initial admission to the hospital, occurring in 83.3% of cases (n=25). In 13 patients (52%) it was located in the epigastric region and in 8 patients (32%) it radiated to the back. The symptoms on admission to hospital is shown in Figure 1.

Drugs were the most common causes of AP in the study population. L-asparaginase was the most frequently identified drug involved in the development of AP. The etiological factors responsible for AP are listed in Table I.

A total of 15 (50%) patients exhibited concurrent medical conditions. These were in the order of frequency: acute leukemia (n=6, 20%), epilepsy (n=4, 13.3%), hereditary spherocytosis (n=1, 3.3%), hyperlipidemia (n=2, 6.7%), Crohn's disease (n=1, 3.3%), and chronic renal failure (n=1, 3.3%).

A review of the family history revealed that 6 (20%) of the parents were first-degree relatives. In addition, one patient's father (3.3%) had a prior diagnosis of AP, although the cause was unknown.

After examination of anthropometric measures, we determined that 13 patients (43.4%) had short stature, 11 (36.7%) exhibited wasting, 13 (43.4%) were underweight, 3 (10%) were classified as overweight, and 2 (6.7%) were obese.

A total of five patients (16.7%) exhibited a fever (>38°C), while one patient (3.3%) demonstrated decreased systolic blood pressure, tachycardia, and tachypnea in accordance with age-specific norms. The physical examination findings revealed the following: abdominal tenderness (n=18, 60%), hepatomegaly (n=6, 20%), splenomegaly (n=5, 16.7%), abdominal distension (n=4, 13.4%), icterus (n=4, 13.4%), and rebound tenderness (n=2, 6.7%).

Serum amylase and lipase levels increased to three times of the upper limit of normal (ULN) level in 86.6% (26/30) and 73.9% (17/23) of the patients, during the follow-up respectively. Four (17.3%) patients had normal amylase levels despite elevated lipase levels. The median amylase levels were 586 U/L (250-2658), representing a fivefold increase above the ULN levels. The median lipase levels were 305 U/L (23-2922), exhibiting a six-and-a-threefold increase above the ULN levels.

Table II presents a comparative analysis of demographic and laboratory findings between patients with biliary disease and non-biliary disease, as well as between patients with drug-induced and non-drug-induced acute pancreatitis. In AP patient group related to biliary disease, median amylase, ALT, AST, GGT, total and direct bilirubin levels were significantly increased (p= 0.021, p<0.001, p<0.001, p<0.001, p=0.004, p<0.001 respectively). The patients with drug-induced pancreatitis had lower ALT, total and direct bilirubin levels than other causes (p= 0.019, p<0.007, p<0.012 respectively).

The USG showed a normal pancreas in 4 (13.4%) or couldn't be assessed in 7 patients (23.4%) because abnormal gas was present. In four of the seven patients, CT scans revealed an enlarged pancreas, decreased echogenicity, or a heterogeneous pancreatic appearance. Of the patients 63.3% had changes on USG, whereas 85% on CT and 70% on MRCP respectively. Radiologic findings were absent in three patients. The findings from the imaging studies are summarized in Table III. The severity of AP is demonstrated in Table IV based on the criteria outlined in the methods.

Treatments administered to the patients included intravenous fluid resuscitation and cessation of oral feeding. Twenty-eight (93.3%) patients received gastroprotective treatment.

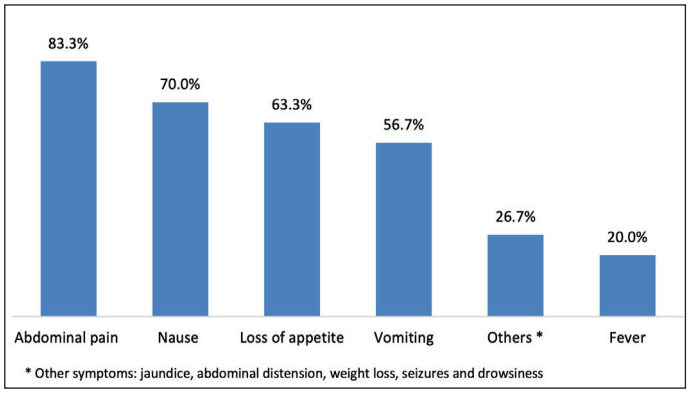

Figure 1: Symptoms of patients

Table I: Causes of acute pancreatitis

Etiology	n (%)
Drugs	9 (30)
L-Asparaginase	4 (13.3)
Valproic acid	2(6.7)
Imipramine hydrochloride	1 (3.3)
Mesalazine	1 (3.3)
Carbamazepine	1 (3.3)
Biliary diseases	8 (26.7)
Gallstone/biliary sludge	6 (20.1)
Choledochal cyst	1 (3.3)
Annular pancreas	1 (3.3)
Infection	5 (16.7)
Mumps	2 (6.7)
Brucella	1 (3.3)
Hepatitis A	1 (3.3)
Ebstein Barr Virus	1 (3.3)
Hyperlipidemia	3 (10)
Idiopathic	3 (10)
Cystic fibrosis	1 (3.3)
Secondary to ERCP	1 (3.3)

ERCP: *Endoscopic Retrograde Cholangiopancreatography*

A nasogastric tube was placed in twenty-five patients (83.3%) for gastric secretion drainage. Three (10%) patients received paracetamol treatment, and six (20%) patients needed meperidine treatment to relieve their abdominal pain. Oral feeding was initiated on median four days (range: 1-30 days) [Polymeric diet (n=9, 30%), MCT diet (n=21, 70%)]. The LOH time of those fed with polymeric diet [median: 8 days (range: 4-34 days)] was significantly shorter than those fed with MCT diet [median: 18 days (range: 4-66 days)] (p=0.036). Oral feeding was started in a median of five days (range: 1-30 days) with polymeric diet, while in three days (range: 2-9 days) with MCT diet.

Total parenteral nutrition was given to six (20%) patients on 4±2.5 days of hospitalization and continued for 20±15.9 days. Median LOH time of the TPN receiving patients [37 days (range: 18-66 days)] was significantly longer than others [13 days (range: 4-40 days)] (p<0.001). A delayed initiation of oral feeding was related with long LOH time (p<0.001).

The mean time for amylase levels to normalize was 9.1±4.6 days, while lipase levels normalized in 11.7±6.9 days.

The complications observed included the formation of pseudocysts in two patients on the 9th and 32nd days of hospitalization, respectively. The previous case was resolved spontaneously, whereas in the latter case, drainage was required. Other complications were noted, including two cases of sepsis (6.7%), as well as one instance of severe electrolyte disturbance. A third patient, who had AP related to hypertriglyceridemia, developed pancreatic necrosis on the 15th day of hospitalization.

There was no mortality attributable to AP. Although the acute pancreatitis was resolved, two patients (6.7%) died because of their underlying systemic disease.

Table II. Demographic and laboratory findings of the patients with acute pancreatitis

	Biliary group (n=8)	Non-biliary group (n=22)	p	Drug-induced group (n=9)	Not drug induce group (n= 21)	p
Female*	3 (37.5)	9 (40.9)	0.723	4 (44.4)	8 (38.1)	0.214
Age (years)†	12.9±4.3 (3-16)	12.2±4.4 (5-18)	1.000	10.9±5.3 (5-18)	13±3.7 (3-18)	1.000
Amylase (U/L)‡	1106 (413-2569)	504.5 (250-2658)	0.021	405 (270-908)	596 (250-2658)	0.164
Lipase (U/L)‡	184 (61-2922)	322.5 (23-2868)	-	292 (23-980)	450 (61-2922)	0.643
ALT (U/L)‡	199.5 (66-468)	15.4 (1-521)	<0.001	14 (1-67)	75 (1-521)	0.019
AST (U/L)‡	113 (28-519)	25.5 (10-1662)	<0.001	26 (15-30)	35 (10-1662)	0.070
GGT (U/L)‡	232 (108-1317)	18.5 (2-548)	<0.001	21 (7-349)	93 (2-1317)	0.263
T. bil (mg/dl)‡	1.9 (0.4-34.6)	0.5 (0.1-4.0)	0.004	0.4 (0.1-1.3)	1.0(0.2-34.6)	0.007
D. bil (mg/dl)‡	0.9 (0.1-26.4)	0.2 (0-3.0)	<0.001	0.1 (0.02-0.4)	0.3 (0-26.4)	0.012
LOH (day)‡	13 (7-40)	17 (4-66)	0.597	18 (6-66)	16 (4-40)	0.533

***:** *n(%) Fisher's Exact Chi-Square test,* **†:** *mean±SD (minimum-maximum) Student's t test,* **‡:** *Median (min-max) Mann Whitney U test,* ***Amylase:** *Pancreatic amylase,* ***ALT:** *Alanine aminotransaminase,* ***AST:** *Aspartate aminotransferase,* ***GGT:** *Gamma-Glutamyl Transferase,* ***T.bil:** *total bilirubin,* ***D.bil:** *direct bilirubin,* ***LOH:** *The length of hospitalization*

Table III. Imaging findings in acute pancreatitis

	Ultrasonography (n=30)	Computed tomography (n=20)	MRCP(n=10)
Enlarged pancreas*	18 (60)	14 (70)	5 (50)
Hypoechoic pancreas*	13 (43.4)	12 (60)	3 (30)
Dilated pancreatic duct*	3 (10)	2 (10)	2 (20)
Peripancreatic fluid*	3 (10)	4 (20)	2 (20)
Pseudocyst*	2 (6.7)	2 (10)	1 (10)
Stones or sludge*	11 (36.7)	3 (15)	4 (40)

***:** *n(%),* ***MRCP:** *Magnetic resonance cholangiopancreatography*

Table IV: Severity of acute pancreatitis

	Number of patients (%)	
	Mild pancreatitis	Severe pancreatitis
Atlanta Criteria	27 (90)	3 (10)
De Banto Criteria	28 (93.3)	2 (6.7)
Ranson and Modified Glasgow Criteria	28 (93.3)	2 (6.7)
Acute Physiology and Chronic Health Evaluation II Criteria	30 (100)	-
North American Society of Pediatric Gastroenterology, Hepatology and Nutrition	26 (86.7)	4* (13.3)

***:** *Moderately severe*

Recurrent pancreatitis was seen in four patients (13.4%) and the number of episodes ranged between two and four. No patient exhibited the evolution of chronic pancreatitis, nor did any patient demonstrate pancreatic insufficiency during the follow-up.

DISCUSSION

Acute pancreatitis is a painful inflammatory condition that leads to significant complications. Over the past 10-15 years, the incidence of acute AP in children has increased due to awareness of the disease and improved access to laboratory and radiologic evaluation (3,5). Abdominal pain, nausea, and vomiting are among the most frequent symptoms in AP patients. The pain is generally in the epigastric region, radiating to the back (3).

Werlin et al. (19), reported that abdominal pain, mostly localized to epigastrium was the leading symptom (67.7%), followed by vomiting (44.8%). Pain radiated to the back was reported to be 9.6% of the children with abdominal pain. Deveci et al. (20) noted that the most frequent complaints at first visit were abdominal pain (94.4%), vomiting (60.2%), malnutrition (36.1%), nausea (17.6%), diarrhea (13%), and fever (13%). Similarly, abdominal pain was also the most common symptom in our study (83.3%), with almost half of the cases localized in the epigastric region and 32% and radiated to the back. Nausea (70%) was the second common symptom and other symptoms were as follows: loss of appetite (63.3%), abdominal tenderness (60%), vomiting (56.7%) and distension (13.4%).

The diagnosis of AP was mainly based on the elevation of pancreatic enzymes. Especially in the first 24 hours after the onset of symptoms, the increase of amylase is more valuable in diagnosis of AP. Lipase is a more specific diagnostic indicator and remains elevated longer than amylase (1). Chlebowczyk et al. (21), reported that amylase values were ≥3 times higher than normal in 63 (82.9%) of 76 acute pancreatitis attacks in 51 children. Lipase values were examined in 28 of these patients and it was determined that lipase values were ≥3 times higher than normal in 19 of them. In our study, serum amylase was increased in 86.6% and lipase levels

was raised in 73.9% of patients. The difference may be because of the fact that serum lipase wasn't measured in all our patients.

The etiology of AP differs in various studies (1). Trauma, medication, systemic diseases, biliary diseases, and infections are at the forefront etiologic factors in children (1, 4). Salim et al. (22), stated that the most common causes of AP were medication (31.2%) gall stone (9%), and idiopathic (32.8%). Sweeny et al. (23), reported the most common etiology as idiopathic (31%), drug use (23%), biliary or gallstones (18%), and viral infection or systemic diseases (17%). In our study, the most common etiologies were drugs (30%), biliary diseases (26.7%) and infections (16.7%). As the patients with trauma related AP are hospitalized in pediatric surgery division, there was no traumatic AP in our study.

Drug history should be carefully questioned in patients with AP because too many drugs have been reported to cause AP. Valproic acid, L-asparaginase, 6 mercaptopurine/azathioprine, corticosteroids and mesalamine have been noted as the most common causes of AP in children (3,24).

The incidence of AP during L-asparaginase treatment ranges from 2 to 18% and repeated doses are reported to increase the risk (25). In our study, L-asparaginase was the most common drug in patients with drug-induced pancreatitis. This may be attributed to the fact that our hospital is a referral center for the treatment and follow-up of children with leukemia.

Valproic acid was the most common drug that led to AP, which may be related to the frequent use in childhood epilepsy due to Werlin et al's study (19). In our study valproic acid was the second most common drug which led to AP.

Gallstones, microlithiasis, bile sludge, sphincter of Oddi dysfunction, pancreatic division, and structural/other abnormalities (choledochal cyst, annular pancreas, mass, or cyst compressing the pancreatic duct) constitute the common biliary causes of childhood pancreatitis (3). Similarly, in our study, biliary causes gallstones and sludge were 75% of biliary causes.

According to Choi BH et al. (26) , serum lipase, ALT, AST, and total bilirubin levels were elevated in the biliary group compared to the non-biliary group. Similarly, our study showed that the biliary group had significantly elevated median levels of amylase, ALT, AST, GGT, and total and direct bilirubin compared to the non-biliary group. Serum ALT, total and direct bilirubin levels of drug-related AP were found to be statistically significantly lower than group that is no drug related due to our findings. This significant difference may be due to inclusion of biliary causes in the non-drug group.

Suvak et al. (27) diagnosed AP secondary to brucellosis in 21 patients among 347 acute brucellosis patients. In our study, a blood culture obtained from the patient who was hospitalized for abdominal pain, vomiting, and fever revealed Brucella infection. In countries like ours where Brucella infection is endemic, brucella-associated AP should be considered when suspected by history and clinic.

The treatment of AP is based on nutrition significantly. It was believed that stopping oral feeding in patients with AP reduced pancreatic secretion 20 years ago. However, early feeding has been shown to reduce pancreatic complications in large, controlled studies (3). In patients with mild pancreatitis, oral nutrition is recommended for the first 24-48 hours (28). The median time to initiate oral feeding in our study was four days (1-30 days). Without enteral nutrition or postpone initiation of enteral nutrition due to the severe course of AP may end with the atrophy of the gastrointestinal tract and increased complications from bacterial translocation. This fact may explain the longer LOH time with delayed initiation of oral feeding. The cases of mild pancreatitis had shorter duration of hospitalization in which a full solid diet was started in the initial treatment (29). In our study, the median hospitalization time was shorter in initially fed with a polymeric formula [8 days (4-34)] compared to MCT-enriched peptide-based formula [18 days (4-66)] (p=0.036). This may be due to a preference for the MCT-enriched peptide-based formula in clinically more severe cases of AP.

CONCLUSION

Acute pancreatitis, although infrequent in childhood, is a critical health problem. Children with abdominal pain, especially those on medications such as L-asparaginase and valproic acid or those with a history of gallstones or biliary sludge, should be evaluated for acute pancreatitis through pancreatic enzyme testing and ultrasonography. The study also suggests that early initiation of nutrition in acute pancreatitis is associated with a shorter hospitalization period.

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Original Article

Changing Face of Pediatric Acute Poststreptococcal Glomerulonephritis in the Pre and Post Pandemic Period: A Comparison Study

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ABSTRACT

Objective: Acute poststreptococcal glomerulonephritis (APSGN) is the leading cause of acute glomerulonephritis in children. APSGN often develops after pharyngitis due to the activation of antibodies and complement proteins to streptococcal antigens by an immune complex-mediated mechanism. In this study, we aimed to analyze APSGN patients diagnosed before and after the pandemic, with their demographic characteristics , clinical and laboratory findings.

Material and Methods: In this study, patients diagnosed with APSGN in a tertiary children's hospital between October 2022 and March 2023 were retrospectively analyzed. The patients were compared with a large cohort followed up with the same diagnosis between 2010-2022. The patients were divided into two groups: group I (n=153, pre-pandemic) and group II (n=28, post-pandemic). Clinical, radiologic, and laboratory findings were compared between the two groups.

Results: The mean age at diagnosis in the group I (2010-2022) was 7.36±2.92 years, and in the group II 8.69±2.51 years. More than three-fourths of the cases [group I/group II; 106 (69.3%) / 21 (71.4%)] were male in both studies. As macroscopic hematuria was the most common finding in the group I, hypertension was the most common finding in group II. Complement 3 (C3) levels were significantly lower in the group I and C3 recovery time was significantly shorter in the group II. Five (19.4%) of patients in group I and only one patient in group II progressed to RPGN.

Conclusion: The incidence of APSGN increased rapidly after the Covid-19 pandemic when the use of face masks was discontinued. Although the patients presented with a serious clinic, their prognosis was better.

Key Words: Acute, Child, COVID-19, Pandemic, Poststreptecoccal glomerulonephritis

INTRODUCTION

Acute poststreptococcal glomerulonephritis (APSGN) is an immune-complex mediated glomerular disease triggered by group A β-hemolytic streptococcus (GAS) or streptococcus pyogenes infections. APSGN primarily affects children aged between 5 and 12 years, and is uncommon among children aged below 3 years (1). The clinical presentation varies from asymptomatic, microscopic or macroscobic hematuria (30-50%) to the acute nephritic syndrome characterized by smoky, and tea or cola colored urine, proteinuria (which can reach the nephrotic range), edema, hypertension (50-90%) and elevation of serum creatinine level. However most children are asymptomatic (2). Rarely, rapidly progressive glomerulonephritis (RPGN) occurs in less than 0.5% of cases and progressed with damage to more than 50% of the glomeruli and formation of crescent formation, and acute kidney injury (AKI) occurs with >50% loss of kidney function within a few days to weeks (3,4). Hypertension has been reported in 50-

Conflict of Interest: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics Committee Approval: This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by the Clinical Research Ethics Committee No. 1 of Ankara Etlik City Hospital (2020-KAEK-141/123).

Contribution of the Authors : ***UZUN KENAN B:*** Constructing the hypothesis or idea of article. Analyzed the results. Planned the methodology to reach the results, examined the patient data. Interpreted the results and discussed them with the current literature. ***ÇAKICI KARGIN E:*** Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***GÜNGÖR T:*** Conducted statistical analysis of the data. ***KARAKAYA D:*** Assisted in collecting patient data. ***ÇELİKKAYA E:*** Assisted in collecting patient data. ***YILMAZ ÇALTİK A:*** Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar.

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90% of cases in various series. in various series (5). Hypertensive encephalopathy is a rare but serious complication (5,6). These patients require emergent intervention.

The estimated global incidence of APSGN is 470.000 cases per-year and APSGN often occurs in regions of the world with poor socio-economic status, with an annual incidence ranging from 9.5 to 28.5 per 100.000 individuals (7). The rate of APSGN has decreased over the last few decades in high-income countries due to the use of antibiotics, improved socio-economic status, and hygiene (8). However, APSGN remains one of the important causes of acute kidney injury (AKI) among the pediatric populations and the leading cause of hospital admission in developing countries (9). However, the nature of the preceding infectious disease is not associated with the clinical course and severity of APSGN. Although the exact mechanisms of glomerular injury in APSGN have not yet been elucidated, they appear to be caused primarily by an autoimmune response to nephritogenic streptococcal antigens. This autoimmune response leads to the formation of immune complexes and activation of the alternative complement pathway, resulting in glomerular inflammation and damage. These antigens activate the alternative complement pathway which often leads to low levels of C3 (10).

The severity of complement activation is an important factor determining the severity of a possible APSGN clinic (11). There is no specific therapy to treat APSGN. Management is supportive and is focused upon treating the volume overload that causes the clinical complications of APSGN. These general measures include sodium and water restriction, and diuretic therapy, but according to the clinical findings immunosuppressive therapy and kidney replacement therapy may be required (4). Most patients, particularly children, have an excellent outcome (12,13). However, APSGN remains among the important causes of hospitalization and acute kidney failure in children (14).

In this study, we aimed to analyze APSGN cases diagnosed before and after the pandemic, with their demographic characteristics and clinical and laboratory findings.

MATERIALS and METHODS

Study population

This present study retrospectively analyzed pediatric patients diagnosed with APSGN between 2010-2022 years and September 2022 and March 2023 in a single-center, tertiary children's hospital. Patients were divided into two groups: group I (n=153, pre-pandemic) and group II (n=28, post-pandemic). Clinical, radiological and laboratory findings were compared between the two groups. The inclusion criteria for the study were 1-18 years of age and ≥ 1 year follow-up. Patients with kidney disease or clinically unproven diagnostic evidence of underlying kidney disease, including chronic kidney disease (CKD), were excluded from the study.

Definition

Evidence of prior streptococcal infection was determined based on the presence of a high ASO level. Patient data retrospectively obtained from medical records included the following: clinical and demographic data, age, sex, symptoms, physical examination findings; including blood pressure at presentation and at each follow-up visit, laboratory findings; including the serum creatinine and urea levels, estimated glomerular filtration rate (eGFR), albumin, potassium, anti-streptococcal antibodies (ASO), and complement factor 3 (C3) and C4 levels, urine microscopy findings and proteinuria values, abdominal ultrasonography (USG) findings, kidney biopsy findings, and treatment method. Renal biopsy was performed in cases with persistent hematuria or proteinuria and persistent azotemia (15).

According to the American Academy of Pediatrics 2017 HT Guidelines, the diagnosis of hypertension (HT) based on office blood pressure (BP) measurement is as follows: HT is defined as the average of three consecutive systolic and/or diastolic BP measurements above the ≥ 95th percentile for age, sex, and height using the auscultation method, or as BP >130/80 mm Hg in participants aged 13 years and older (16).

Oliguria was defined as 1 ml/kg/hr in infants or 0.5 ml/kg/hr or <500 ml/day in children. An estimated glomerular filtration rate (eGFR) was calculated according to the Schwartz formula (17). Protein excretion in urine was defined by non-nephrotic (spot urine protein/creatinine ratio > 0.2 or 24-hour urine protein excretion of -40 mg/m^2/hour) or nephrotic (spot urine protein/creatinine ratio >2 or 24-hour urine protein excretion >40 mg/m^2/hour) ranges (18).

Hematuria was defined as the presence of more than 5 erythrocytes in a microscopic field in the urine sediment. The values of C3 <0.76 g/L and C4<10 mg/dL were considered low. A low albumin level was defined as <2.5 g/dL. Evidence of prior streptococcal infection was determined based on the presence of a high ASO titer and ASO level >200 UI /mL were considered abnormally high. Magnetic resonance imagination (MRI) was performed in patients with central nervous system involvement. Treatment data included diuretics, antihypertensives, benzathine penicillin, fluid restriction, corticosteroids, and renal replacement therapies. The study was approved by the Clinical Research Ethics Committee No. 1 of Ankara Etlik City Hospital (2022-KAEK-141/123).

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows version 22.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov–Smirnov test was used to determine the normality of the distribution of the study variables. Parametric variables are shown as mean and standart deviation, and nonparametric variables were shown as median (range). Categorical data presented as frequency and percentage. Student's t test was used to compare parametric variables and the Mann–Whitney U test was used to compare nonparametric variables. The χ^2 test or Fisher's exact test was used to compare categorical variables. The level of statistical significance was set at p<0.050.

RESULTS

The cases were defined as group I (pre-pandemic) and group II (post-pandemic), and the findings were evaluated together.

A total of 153 patients in the 1st group and 28 patients in the 2nd group were analyzed retrospectively. In both groups, two thirds (2/3) of cases were male [n=106 (69.3%), n=20 (71.4%) respectively]. There was no significant difference between the patient groups in terms of gender (p=0.800). As the mean age of group I was 7.36±2.92 years, the mean age of group II was 8.69±2.51 years and group II was significantly older (p=0.020). Upper respiratory tract infection (URTI) was reported at similar rates in both groups, n=138 (90.2%), n=27 (95.7%). There was no statistically significant difference between the patients in terms of history of pharengytis (p=0.438), pyoderma (p=0.086) and antibiotic use (p=0.740) between both of groups.

Clinical findings were analyzed in both groups. Macroscopic hematuria (p=0.010) was significantly more common in the 1st group, while hypertension (p=0.010) was significantly higher in the 2nd group. Macroscopic hematuria recovery time was significantly shorter in the 2nd group, which had a better clinical course (p<0.001). There was no significant difference between the groups in terms of microscopic hematuria (p=0.300), peripheral edema (p=0.300), and nephrotic proteinuria (p= 0.580). Oliguria was observed in 13 (46.4%) patients, however anuria was not reported. Hypertensive encephalopathy was observed in only one patient in the 2nd group and the patient was treated in the pediatric intensive care unit. Cerebral imagining (magnetic resonance imaging) was performed for hypertensive encephalopathy. In the 1st group, one fifth of the cases 19 (12.4%) progressed to RPGN, while in 2nd, one patient (3.5%) progressed to RPGN. There was no statistically significant difference in the patient groups in terms of RPGN prognosis (p=0.160).

The cases were analyzed in terms of laboratory findings. There was no significant difference between the groups in terms of serum creatinine levels (p=0.070), but glomerular filtration rate (GFR) was significantly high and GFR recovery time wassignificantly shorter in 2nd group (p=0.010). Complement levels were analyzed as C3 and C4, and C3 recovery time was significantly shorter in the 2nd group (p=0.001). The logistic regression analysis revealed that age and gender are not significant risk factors for the development of AKI (p=0.620, p=0.100, respectively). Initially, hypertension, nephrotic proteinuria, and macroscopic hematuria were not determined as significant risk factors (p=0.740, p=0.220, p=0.720, respectively). Complement 3 (C3) and albumin levels were also not determined as significant risk factors (p=0.900, p=0.170, respectively). Baseline characteristics of patients in pre and post-pandemic study were seen in Tablo I.

Antibiotic therapy was given to almost all cases in both groups (90.1%, 96.4% respectively). There was no statistically significant difference in the patient groups in terms of time of hospital stay (p=0.550).

Diuretic treatment was used in both groups [group I/group II; n=105 (68.6%), n=22, (78.6%)] approximately two-thirds (2/3) of the cases. Approximately one fourth (26.1%) of the patients in the 1st group and one third (28.6%) of the patients in the 2nd group required a second antihypertensive drug (nicardipine). Eighteen (11.8%) patients in the 1st group and only one patient in the 2nd group treated corticosteroids. In the 1st group, nine (5.9%) patients required renal replacement therapy (RRT) and hemodialysis was the preferred modality. None of the patients required RRT in 2nd group. Demographic and clinical features were given in Table II.

Tablo I: Baseline characteristics of patients in pre and post-pandemic study

Characteristic	Group I Pre-pandemic (n=153)	Group II Post-pandemic (n=28)	p‡
Gender male*	106 (69.3)	20 (71.4)	0.800
Patient age, years†	7.36±2.92	8.69±2.51	0.020*
Macroscobic hematuria*	116 (75.8)	18 (64.3)	0.010*
Microscobic hematuria*	37 (24.2)	10 (35.7)	0.300
Peripheral edema*	105 (68.6)	9 (32.1)	0.300
Hypertension*	66 (43.1)	24 (85.7)	0.010*
Nephrotic proteinuria*	54 (35.3)	18 (64.3)	0.580
Macroscobic hematuria, days†	10.81±7.38	4.57±3.70	0.000*
Hypoalbuminemia*	7 (4.6)	3 (10.7)	0.550
Hospitalization*	109 (71.2)	27 (96.4)	0.550
Serum creatinine, mg/dl†	1.15±1.08	0.78±0.31	0.070
C3 recovery time days†	63.68±69.29	38.04±24.21	0.001*
eGFR (ml/min/1.73 m²)†	65.13±28.94	80.29±25.32	0.010*
eGFR, recovery time days†	21.3±28.54	11.61±16.70	0.010*
Hospitalization, time days†	5.85±5.54	6.53±3.17	0.550
RPGN progression*	19 (12.4)	1 (4.3)	0.160

:** *n(%),* **†:** *mean ± SD,* **‡:** *Student's t test,x² sher' exact test,* ***C3: *complement 3,* ***eGFR:*** *mestimated glomerular filtration rate,* ***RPGN:*** *rapidly progressive glomerulonephritis.*

Table II: Demographic and clinical features of APSGN in children

	Group I Pre Pandemic	Group II Post-Pandemic	p†
Year of study	2010-2022	2022-2023	
Type of study	Retrospective	Retrospective	
Sample size, n	153	28	
F/M ratio	1:2.25	1:2.5	0.800
Hypertension*	66 (43.1)	24 (85.7)	0.010*
Ensephalopathy*	3 (3.9)	1 (4.3)	0.939
AKI*	68 (44)	18 (64.3)	0.057
Pyoderma releated*	15 (9.8)	1 (4.3)	0.009
Pharyngitis releated*	138 (90.2)	27 (95.7)	0.438

**: n(%),†: Student's t test, x^2 sher' exact test*

DISCUSSION

APSGN is the most common acute glomerulonephritis in children worldwide (19). There are over 470.000 cases of APSGN that occur annually leading to approximately 5000 deaths, with 97% of these cases in less developed countries (20). The annual incidence of APSGN is estimated to be 9.3 cases per 100.000 population in developing countries (21). In the Karakaya's single-centered study between 2010 and 2022, the frequency of APSGN was 1 case/month (22).

In our study, a very high number of newly diagnosed APSGN cases, such as an avarage of 4.6 cases per month, were observed. Although it is stated in the literature that there is a decrease in glomerulonephritis cases due to successful vaccination programs (23). However, we have reported a rapid increase in APSGN cases in our recent post-pandemic study. This can be explained stop to use of face mask after the Covid- 19 pandemics. However, it is possible that different streptococcal strains encountered after the pandemic may be the reason for the clinical difference in increasing APSGN cases. APSGN is common in the 5-12-year-old age group (1). In the study of Becguet et al. (23), the median age of APSGN cases was 6.7 and Gunasekaran et al. (24) was 6.8 years age (25). Although the mean age at diagnosis of the patients (8.69±2.51years) were older than in the literature, it was also significantly older than in 1st group (p=0.020). APSGN has a two-fold higher incidence in males in females (24,26,27). In our study, male gender was dominant in terms of gender ratios in both groups, like the literature (2.5/1). In the both groups in our studies the most frequently reported infection was URTI. Evidence that antibiotic therapy protects against the development of glomerulonephritis following streptococcal infection is conflicting (28-30). In both of our groups, antibiotic prophylaxis was given to almost all of the cases (90.1%/95.8%) for URTI. Although antibiotics are not routinely used in the treatment of APSGN, prophylactic treatment with an antibiotic covering the GAS spectrum is recommended to prevent the spread of nephritis-associated streptococcal infection (12). Hypertension is a very common complication in APSGN and often requires treatment. The prevalence of hypertension in various case series can range from 64%, to as high as 82.4%, to 92% (24,25,31). In our pre-pandemic study, macroscopic hematuria was the most common clinical finding, however in the post-pandemic study, hypertension (85.7%) was significantly the most common (p=0.010). Hypertension in APSGN is of the low renin type and is typically mild and biphasic, caused by water retention (32). Evidence of edema is particularly observed in cases before and after the pandemic. While there was no statistically significant difference between the patient groups, the increased frequency of hypertension supports a possible synergistic effect with potential pathophysiological mechanisms (33,34). In our study, approximately 63.4% of patients in the covid-19 center tested positive for covid-19 in the past six months, providing strong evidence for this hypothesis. Although we were not able to examine the strain of GAS in this study, the GAS strain, which is probably less virulent and better prognosis, caused the current APSGN clinical and laboratuary findings. Additionally, it is possible that the GAS strain may increase both the frequency of the disease and the risk of developing hypertension (35). In some series, cerebral complications related to hypertension have been reported in 30-35% of children with APSGN (9,31,36). In our study, one case was treated in the pediatric intensive care unit with generalized seizures and hypertensive encephalopathy. In the literature, nephrotic proteinuria has been reported in different series, ranging from 1.48%, 18%, 25% and 32% (24,25,31,36). As nephrotic proteinuria was seen in half of the cases in the pre-pandemic group, it was seen in 2/3 of the cases in the post-pandemic group. This condition more severe clinical course, but it regressed to non-nephrotic range within 2 weeks. However, APSGN is still one of the important causes of AKI and hospitalization in children (11). Studies have shown that AKI observed at rates ranging from 13.3% to 43.7% (12,37). In our study, AKI observed in two third (64.3%) of the cases, but none of the cases required dialysis. A study of adults determined both persistent hypertension and nephrotic proteinuria to be predictors of AKI (38). Gunasekaran et al. (25) found hematuria to be a predictor for AKI. However, in our post-pandemic study no correlation was found between the development of AKI and the presence of hematuria, hypertension or nephrotic proteinuria. Hematuria is seen in virtually all patients with APSGN. Individually evaluating the clinical findings showed that macroscopic hematuria is observed in 30–50% (12). In our study, macroscopic hematuria was observed as the second most common finding in approximately 64.3% (n=18) of the patients. Nephrotic proteinuria, hypertension, and macroscopic hematuria were seen at higher rates in this study compared to the literature and pre-pandemic studies. It may be a result of the immunological features of the releated GAS strain and rapidly developing but self-limiting complement activation (11,39).

Complement 3 level is a very important blood biomarker with nephritic-associated clinical features and activation of the alternative complement pathway in APSGN. The serum C3 level was low in 90% of the cases (11). In the pre-pandemic study, it was determined that disease severity and prognosis were positively correlated with the severity of complement activation. However, in the literature, C3 level Information on the relationship between and RPGN is variable. It is reported that the level of complement C3 fraction is lower in patients with a severe clinical course (12). However, another study reported that there was no relationship

between C3 fraction and the clinical course of RPGN (40). In our recently published pre-pandemic study, which reported the relationship between severe clinical features of APSGN (progress to RPGN), we found that especially low C3 and albumin levels and high CRP, PLR, CRP/albumin ratio and ESR, as well as nephrotic level proteinuria, are associated with APSGN (22). They have been found to be determinants of poor prognosis in children and have been identified as predictive factors in the progression of APSGN to RPGN (22). The significantly shorter post-pandemic C3 level recovery time compared to the first group is associated with a better clinical course. The APSGN prognosis was better in our post-pandemic study. We could not analyzed the type of GAS in our study, but it suggested the hypothesis that a possible more less virulent GAS strain or the strong immunity of the host causes a more benign clinical course. A recent study reported in South Korea reported that the degree of decrease in serum C3 level was milder in children with APSGN in recent years and that was associated with a decreased rate of acute nephritic features (11). This finding strongly supported our possible hypothesis.

Treatment of APSGN is completely symptomatic and comprise monitoring of fluid balance, blood pressure, body weight and the serum creatinine and electrolytes (9,41). Loop diuretics can be used if volume increase and loading findings are detected. Calcium channel antagonists can be used to treat HT (41). Antibiotics are not routinely used in APSGN, but prophylactic treatment with antibiotics is recommended for patients with signs of streptecoccal infection. Antibiotic therapy does not change the course of the disease, but from an epidemiological point of view it is very important to prevent the spread of nephritis (12). Long term antibiotic prophylaxis is not justified since recurrence of APSGN are very rare (42). In this study diuretic therapy (furosemide) was prescribed in three fourth of cases (75%) and a second anti-hypertensive drug (nicardipine) was given to 37.5% (n=6) of children, as in earlier studies (27,37,42). Only 8.3% patient treated three or more antihypertensives. Antibiotics are not routinely used in the treatment of APSGN, but prophylactic treatment with an antibiotic covering the GAS spectrum is recommended to obstruct the spread of nephritis-associated streptococcal infection. Additionally, in both groups the present study almost all of the cases (>90%) were treated antibiotics. Medical treatment of RPGN consists of corticosteroids and renal replacement therapies. In the literature, it has been reported that adult RPGN patients treated with corticosteroids have an excellent result, but the time of treatment is variable (43). We treated with corticosteroids our cases that progressed to RPGN in both groups, and with early diagnosis and treatment, chronic kidney damage (CKD) was not observed in any case.

In conclusion, APSGN continues to be a significant health problem in developing countries. Compliance with mask-wearing and hygiene recommendations emerges as the main factor in APSGN prevention. This study aimed to highlight the increased number of cases and different clinical presentations by comparing APSGN cases before and after the Covid-19 pandemic. The mean age of our patients was older. Hypertension was the most remarkable finding in the present study. Additionally, it is noteworthy that a significant portion of the cases (64.3%) had recently experienced a Covid-19 infection, which may have an impact on the clinical findings.

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Original Article

Evaluation of Parents' Opinions About the Fear of Inhaler Corticosteroid Treatment in Child Patients Diagnosed with Asthma

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ABSTRACT

Objective: The aim of our study was to determine concerns and fears of parents of children with asthma towards the use of ICS, and its' impact on asthma management.

Material and Methods: This prospective study was conducted between 01.04.2023 and 01.06.2024, at the Dr.Burhan Nalbantoğlu Hospital, The Pediatric Immunology and Allergy Clinic, and patients who had been followed up with asthma diagnosis, were included.

Results: There was 100 patients in our study. Out of 100 patients, 67 (67%) were male. The median age of the children was 84.5 months (IQR,73.2-119.5). The median age of asthma diagnosis was 65.5 months (IQR, 24-76.75). All of the patients were using asthma maintenance therapy, and 87 (87%) patients were using it regularly. Out of 100 parents, 78 (78%) had fear and concern of potential adverse effects of using inhaled corticosteroid treatment long time in their children. The most common fears and concerns were described as causing weight gain in 34 (34%) parents, dependance to drug in 33 (33%) parents, and causing growth retardation in 27 (27%) parents. Patients having fear of corticosteroid tended to have difficulties in medicine use (p=0.001). Patients not knowing the treatment of asthma, and not knowing the role of corticosteroid in asthma tended not to have fear of corticosteroid treatment (p=0.046, and 0.001 respectively).

Conclusion: In our study, 78% of the parents had fear and concern of potential adverse effects of inhaled corticosteroid treatment. The most common fear and concerns were about weight gain, dependance to drug, and growth retardation.

Key Words: Asthma, Child, Corticophobia

INTRODUCTION

Asthma is the most common chronic disease seen in children and its prevalence is increasing (1). Childhood asthma prevalence is ranged from 2.1% in developing to 32.2% in developed countries (2). Asthma is a heterogenous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms, such as wheezing, shortness of breath, chest tightness and cough, that vary over time and in intensity, together with variable expiratory airflow inflammation (3).

Long-term goals of asthma management are to achieve good symptom control, and minimize the future risk of asthma-related mortality, exacerbations, persistent airflow limitation and side-effects of treatment. Inhaled corticosteroid (ICS) is the first line recommended controller drug for asthma treatment (3). Non-adherence to ICS is common and can result in persistent symptoms, cause increase in mortality and morbidity of asthma, cause increase in the number of missed school days, and increase the urgent health-care visits. If parents understand the importance of inhaled corticosteroid treatment in asthma treatment, it will increase the compliance of the treatment, reduce patients' symptoms, and reduce their emergency visits. Parents' inadequate knowledge about the nature of the disease and asthma medications, as well as having fears and concerns about the potential adverse effects of ICS treatment, may contribute to non-compliance with the treatment (4). In the literature, there were few studies published on this subject (5-9).

Conflict of Interest : On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics Committee Approval : This study was conducted in accordance with the Helsinki Declaration Principles. This study was approved by the Dr. Burhan Nalbantoğlu Ethics Committee (approval number: EK 14/24).

Contribution of the Authors : ***METBULUT AP:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar.

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The aim of our study was to determine the fears and concerns of parents of children with asthma, towards the use of ICS, and its' impact on asthma management.

MATERIALS and METHODS

The study was conducted between 01.04.2023 and 01.06.2024, at the Dr. Burhan Nalbantoğlu Hospital, The Pediatric Immunology and Allergy Clinic, and patients who had been followed up with asthma diagnosis, were included. Inclusion criteria of the patients were determined as followed-up in the clinic with asthma diahnosis, and being between 6 and 18 years age. Asthma was diagnosed according to the Global Initiative for Asthma guideline (GINA). For symptom control analyse, GINA assessment of asthma control for children 6 years and above were used. The frequency of asthma symptoms (days per week), any night waking due to asthma or limitation of activity, and for patients using a SABA reliever, frequency of its use for relief of symptoms were asked for the past 4 weeks. The treatment of asthma was classified according to the step treatment in GINA guideline. The asthma attack was identified as a change in symptoms and lung function from the patients' usual status according to GINA guideline (3). The exclusion criteria were having chronic respiratory illness rather than asthma, having history of prematurity, having corticosteroid treatment for other reasons, and being above 18 years age, and below 6 years age.

We collected data from medical records including medical history, demographic information such as age, gender, having additional allergic disease, and chronic disease, and symptoms, physical examination, laboratory findings, treatment and hospitalization for asthma.

The scale, prepared by the researcher, evaluating parents' opinions about the fear and concern of corticosteroid treatment in patients diagnosed with asthma, was applied to the parents by the researcher during the outpatient clinic visit. In this scale, asthma disease, its symptoms, treatment, application methods of treatments, the role of corticosteroid treatment in asthma, parents' reasons for fear and concern of potential adverse effects of corticosteroid use, whether they terminated the treatment due to anxiety/fear, their knowledge about the side effects of corticosteroid treatment, difficulty in using asthma treatment. Additionally, parents' quality of life based on education and financial status were questionned. The parents chose answers from options provided.

The G*power 3.1.9.4 analysis program was used to calculate the sample size of this study. It was determined that at least 96 parents should participate in the sample of this study with an effect size of 0.30, a margin of error of 0.05%, df= 96 and 90% power. In total, one hundred parents participated in this study.

This study was approved by the Dr. Burhan Nalbantoğlu Ethics Committee (EK 14/24-15.04.2024). Informed consent was obtained from all participants. Informed consent was taken from the patients' parents.

Statistical Analysis:

IBM Statistical Package for the social sciences, version 22.0 (SPSS Inc., Armonk, NY, IBM Corp., USA). Results were expressed as percentile (absolute numbers), as mean and standard deviation, or as median and interquartile range (IQR) as required. Chi-square test was performed to compare the categorical variables, Mann-Whitney test was used to compare the non-normally distributed continuous variables, and the independent t-test was used for normally distributed continuous data. p value < 0.050 was considered statistically significant.

RESULTS

There was 100 patients in our study. Out of 100 patients, 67 (67%) were male. The median age of the children was 84.5 months (IQR,73.2-119.5). The median age of asthma diagnosis was 65.5 months (IQR, 24-76.75). Sixty-five (65%) patients had diagnosed with wheezy child, the symptoms in these children continued after the age of six, and they continued to be followed with the diagnosis of asthma. The median of the duration between asthma diagnosis and the questionnaire interview was 33.5 months (IQR,7.2-64). Sixty (60%) patients had concomitant allergic diseases. Fifty-nine (59%), two (2%), and one (1%) had allergic rhinitis, food allergy and drug allergy respectively. Skin prick tests (SPT) were performed in 95 (95 %) patients. Fifty-five (55%) of them had aeroallergen sensitivity. Commonly pollen allergen was detected with a rate of 39%. Three (3%) had concomitant chronic disease, one diagnosed with epilepsy, one with congenital heart disease, and one with tracheosaphageal atresia. Fifty (50%) patients' family members had allergic disease, commonly mothers with a diagnosis of asthma with a rate of 29% (Table I). Educational status and their current standard on living based on monthly salary were shown in Table II.

All of the patients were using asthma maintenance therapy, and 13 (13%) patients were using it irregularly. Three (3%) patients were using asthma medication with wrong technique. According to GINA, patients were using maintenance therapy commonly at step one with a rate of 70% (n=70). While taking the medication, 91 (91%) patients were using metered dose inhaler, and 5 (5%) patients were using dry-powder inhaler. Sixty-six (66%), 16 (16%), 14 (14%), and four (4%) patients were using only ICS, both ICS and leukotriene antagonist, both ICS and LABA, and only leukotriene antagonist treatment (Table III).

According to GINA guideline, in the last 3 months, 70 (70%), 21 (21%), and 9 (9%) patients were defined as well controlled, partly controlled, and uncontrolled respectively. Twenty-three (23%) patients had asthma attack in the past one year, and 12 (21%) were hospitalized due to the asthma attack in the past one year (Table III).

Parents perceptions about symptoms related with asthma were questionned. Cough was defined in 80 (80%) parents, dyspnea in 75 (75%), and wheezing in 55 (55%) parents. Parents described that cough was worsened at night in 68 (68%) patients, and at the early morning in 32 (32%) patients (Table IV).

Questions about pathogenesis and triggers of asthma were asked to the parents. Fifty-six (56%) parents defined the asthma as airway narrowing, 37 (37%) as noisy breathing, 35 (35%) as inflammation, 27 (27%) as smoke reaction, 24 (24%) as infections. Twenty-one

(21%) parents mentioned that they had no information about this issue (Table IV).

The treatment of asthma knowledge of parents were questionned. Inhaled corticosteroid, bronchodilators, leukotriene antagonists, and systemic corticosteroid were known as medications of asthma in 72 (72%), 61 (61%), 46 (46%), and 28 (28%) parents. Nineteen (19%) parents described antibiotics for asthma treatment. Eight (8%) parents mentioned that they did not know any type of medicine for asthma. Among these eight parents, all of their children were using asthma maintenance therapy, and 37.5% (n=3) were using it irregularly (Table IV).

Out of 100 parents, 51 (51%) parents stated that inhaled corticosteroid treatment controls asthma symptoms, 45 (45%) stated that prevents asthma exacerbations, 39 (39%) parents stated that relieves bronchial constriction, 22 (22%) stated that reduces airway inflammation, and 16 (16%) stated that strengthens the lung. Twenty-seven (27%) mentionned that they had not known about role of corticosteroid in asthma treatment (Table V).

Out of 100 parents, 78 (78 %) had fear and concern of potential adverse effects of using inhaled corticosteroid treatment long time in their children. The common fear and concerns were described as causing weight gain in 34 (34%) parents, causing dependance to drug in 33 (33%) parents, causing growth retardation in 27 (27 %) parents (Table V).

Among 100 patients who were using maintenance therapy, 53 (53%) patients had difficulties in using medications. The common difficulties were defined as relutance to use (27 [27%]), as being expensive (23 [23%]), as inability to use medication regularly (20 [20%]) (Table V).

Table I: Characteristics of study population

Gender	
Male*	67 (67)
Female / Male	0.49
Age†	
Age (months)	84 (73-117.25)
The age of asthma diagnosis (months), mean, (IQR)	64.5 (24-76.75)
Concomitant Allergic Diseases*	
Allergic rhinitis	59 (59)
Food allergy	2 (2)
Drug allergy	1 (1)
Family member having allergic disease	50 (50)
Asthma	29 (29)
Allergic rhinitis	26 (26)
Food allergy	1 (1)
Atopy status*	
Patients performed skin prick test	95 (95)
Aeroallergen sensitization	55 (55)
Pollen	39 (39)
House dust mite	38 (38)
Mold	14 (14)
Cat dander	15 (15)
Dog dander	5 (5)
Cockroach	3 (3)

***:** *n(%),* **†:** *median, (IQR)*

Table II: Demographic characteristics of the parents

Educational status*	
Primary school graduate	11 (11)
Secondary school graduate	13 (13)
High school graduate	36 (36)
University graduate	40 (40)
Current standard on living based on monthly salary*	
Low	16 (16)
Medium	79 (79)
High	5 (5)

***:** *n(%)*

Table III: Characteristics of clinic and treatment of the patients

Gina Assessment of Asthma in The Last 3 Months*	
Well controlled	70 (70)
Partly controlled	21 (21)
Uncontrolled	9 (9)
Patients having asthma attack in the past 1 year	23 (23)
Patients hospitalized in the last one year for asthma attack	12 (12)
Treatment*	
Only using Inhaled corticosteroids (ICS)	66 (66)
Only using Anti-leukotrienes	4 (4)
Both using ICS and anti-leukotrienes	16 (16)
Both using ICS and LABA	14 (14)
Treatment step according to GINA*	
Step 1	70 (70)
Step 2	1 (1)
Step 3	29 (29)

***:** *n(%)*

Out of 100 patients, 13 (13%) patients were using maintenance therapy irregularly. Seven (53.8%) of patients had stated that they had difficulties in using treatment. Eight (61.5%) patients had fear and concern of corticosteroid treatment. There was statistically significant difference between using asthma maintenance therapy irregularly and not knowing both asthma treatment and the role of corticosteroid treatment in asthma. Patients tended to use more irregulary in patients who did not know both asthma treatment and the role of corticosteroid treatment in asthma (p=0.032, and 0.003 respectively). There was no statistically difference between using irregularly and having fear of inhaled corticosteroid treatment (p=0.125).

There was statistically significant difference between having fear of inhaled corticosteroid treatment and having difficulties of using asthma treatment. Patients having fear of corticosteroid tended to have difficulties in using asthma maintenance therapy (p=0.001). There was no statistically significant difference between having fear of inhaled corticosteroid treatment, and gender, age, parents' educational level, social status, the duration time between asthma diagnosis and questionnaire evaluation, having concomitant allergic disease, having aeroallergen positivity, GINA treatment step, GINA symptom control status, having asthma attack, and having hospitalization (Table VI).

There was statistically significant difference between having fear of corticosteroid treatment, and knowledge of information about treatment of asthma, and knowledge of the role of corticoseroid

Table IV: Parents' perceptions about asthma symptoms, mechanisms, treatment and routes of administration	
Asthma Symptoms known by parents*	
Cough	80 (80)
At night	68 (68)
At early morning	32 (32)
Wheezing	55 (55)
Dyspnea	75 (75)
Early morning chest tightness	30 (30)
The pathogenesis and triggers of asthma known by parents*	
Airway narrowing	56 (56)
Noisy breathing	37 (37)
Inflammation	35 (35)
Smoke reaction	27 (27)
Infections	24 (24)
Others	2 (2)
Don't know	21 (21)
Treatment of asthma known by parents*	
Inhaled steroids	72 (72)
Bronchodilator	61 (61)
Leukotriene antagonist	46 (46)
Systemic steroids	28 (28)
Antibiotics	19 (19)
Don't know	8 (8)
Routes of administration of asthma medicine known by parents*	
Oral	66 (66)
Nebulizer	62 (62)
Inhaler	46 (46)
Injection	16 (16)
Don't know	6 (6)

*: n(%)

Table V: Parental opinions about inhaler corticosteroid treatment in asthma	
Role of inhaler corticosteroid in asthma treatment*	
Know	73 (73)
Control asthma symptoms	51 (51)
Prevent asthma exacerbations	45 (45)
Relieve bronchial constriction	39 (39)
Reduce airway inflammation	22 (22)
Strengthen the lung	16 (16)
Don't know	27 (27)
Concerns about long term use of inhaler corticosteroid*	
Not having fear/concern	22 (22)
Having fear/concern about side effects	78 (78)
Weight gain	34 (34)
Dependence to drug	33 (33)
Growth retardation	27 (27)
Causing organ damage	24 (24)
Need for larger doses later on (become less effective)	23 (23)
Decrease immunity, and cause infection	22 (22)
Causing teeth problems	22 (22)
Bone weakness	16 (16)
Causing hyperreactivity	10 (10)
Causing skin problems	9 (9)
Developing cancer	7 (7)
Difficulties of inhaled corticosteroid (ICS) use*	
Not having difficulties in using maintenance treatment	47 (47)
Having difficulties in using maintenance treatment	53 (53)
Reluctance to use medication	27 (27)
Cost (expensive)	23 (23)
Inability to use medication regularly	20 (20)
Forgetting in using it	16 (16)
Problems with using inhaler devices	15 (15)

*: n(%)

treatment in asthma. Patients not knowing the treatment of asthma, and not knowing the role of corticosteroid in asthma tended not to have fear of corticosteroid treatment (p=0.046, and 0.001 respectively) (Table VII).

DISCUSSION

In this study, 100 pediatric asthma diagnosed patients were included. Out of 100 parents, 78 (78%) had fear and concern of potential adverse effects of using corticosteroid treatment long time in their children. The most common fears and concerns were described as causing weight gain in 34 (34%) parents, causing dependance to drug in 33 (33%) parents, and causing growth retardation in 27 (27%) parents. Fifty-three (53%) patients had difficulties with using medications. The most common difficulty was defined as reluctance to use with a rate of 27%. Patients having fear of corticosteroid tended to have more difficulties in using maintenance therapy. Thirteen (13%) patients were using maintenance therapy irregularly. Patients tended to use more irregulary in patients who did not know both asthma treatment and the role of corticosteroid treatment in asthma. Patients not knowing the treatment of asthma, and not knowing the role of corticosteroid in asthma tended not to have fear of corticosteroid treatment.

According to World Health Organization, in developed countries, adherence to medicine among patients having chronic diseases were 50% (10). Adherence rates to medications in asthma were observed to range between 30-70% of patients (11). Non-adherence to therapy commonly concludes from inadequate knowledge about the disease, and its' treatment, occurence of side effects, and inadequate caregiver communications (4). In our study, 13 (13%) patients were using maintenance therapy irregularly. Eight of them had fear and concern of inhaled corticosteroid treatment. Patients not knowing both the asthma treatment and the role of corticosteroid treatment in asthma, tended to use maintenance therapy irregularly.

According to GINA, ICS is a preferred controller treatment (3). The minimum effective dose of ICS is recommended to avoid possible side effects of corticosteroids. Side effects are commonly local side effects like oral candidiasis, dental caries, and dysphonia. These side effects can be prevented by rinsing mouth and face after inhalation, using correct inhaler technique, and using chamber with valve (12). In a pediatric study, 53% of the parents reported their concern about side effects (5). In another pediatric study, 65.5% of parents were observed to worry about the long-term effects of ICS (13). In our study, 78% of the parents had fear and concern of potential adverse effects of inhaled corticosteroid treatment. Although having high rate of fear and concern, the rate of patients using treatment regularly were observed to be high in our study.

Table VI: Evaluation of having fear/concern of long term use of inhaler corticosteroid treatment according to characteristics of the patients

	Having fear of long term use of inhaler corticosteroid n=78	Not having fear of long term use of inhaler corticosteroid n=22	p
Age of the patients, median, months	84	90	0.515†
Gender, Male*	49 (62.8)	18 (81.8)	0.094‡
The duration time between asthma diagnosis and questionnaire evaluation, median, months	45	18	0.396†
Patients having concomitant allergic disease*	50 (64.1)	10 (45.5)	0.115‡
Patients having allergic rhinitis*	50 (64.1)	9 (40.9)	0.051‡
Patients having aeroallergen sensitization*	42 (53.8)	13 (59.1)	0.720‡
Education level of family* Primary school education Secondary school graduate High school graduate University graduate	8 (10.3) 10 (12.8) 26 (33.3) 34 (43.6)	3 (13.6) 3 (13.6) 10 (45.5) 6 (27.3)	0.566‡
Current standart on living based on monthly salary* Low Medium High	9 (11.5) 65 (83.3) 4 (5.1)	7 (31.8) 4 (63.6) 1 (4.5)	0.072‡
Patients' asthma control status according to GINA assesment* Well controlled Partially controlled Non-controlled	56 (71.8) 15 (19.2) 6 (7.7)	13 (59.1) 6 (27.3) 3 (13.6)	0.431‡
Patients' asthma treatment* Only using Inhaled corticosteroids (ICS) Only using Anti-leukotrienes Both using ICS and anti-leukotrienes Both using ICS and LABA	54 (69.2) 2 (2.6) 12 (15.4) 10 (12.8)	12 (54.5) 2 (9.1) 4 (18.2) 4 (18.2)	0.199‡ 0.168‡ 0.752‡ 0.522‡
Step of asthma treatment* Step 1 Step 2 Step 3	56 (71.8) 1 (1.3) 21 (26.9)	14 (63.6) 0 8 (36.4)	0.615‡
Having difficulties of asthma medication use*	48 (61.5)	5 (22.7)	0.001‡

***:** *n(%),* **†:** *Mann-Whitney test,* **‡:** *Chi-square test*

Table VII: Evaluation of having fear of inhaler corticosteroid treatment according to knowledge about asthma diseases and treatment

	Having fear of corticosteroid treatment n=78	Not having fear of corticosteroid treatment n=22	p†
Not knowing the asthma disease*	15 (19.2)	6 (27.3)	0.413
Not knowing the treatment of asthma*	4 (5.1)	4 (18.2)	0.046
Not knowing the routes of the asthma treatment*	4 (5.1)	2 (9.1)	0.489
Not knowing the role of corticosteroid in asthma*	12 (15.4)	15 (68.2)	0.000

***:** *n(%),* **†:** *Chi-square test*

In a study, in 603 adult asthma diagnosed patients, 53% of the patients (47% of ICS users) stated that they had fear of using ICS. Commonly fears in regard to ICS, were causing weight gain, decreasing in bone density, and a reduction in efficacy of medication over time (4). In a study, 42% of the mothers had concern in their asthma diagnosed children about weight gain due to ICS (14). Unlike these findings, in an another study, 5% of the parents had concern of weight gain due to ICS in their children with asthma (5). A meta-analysis in pediatric population observed that ICS has no effect on patients' body weight index (15). These different concerns rates may have been obtained due to cultural differences in ideal weight and body perception. In our study, the most common fear and concerns was also weight gain with a rate of 34%.

In a study, it was observed that 29% (n=84) of the parents had fear of 'inhaler dependency' in their asthmatic children (16). According to Zedan, it was observed that 9% of parents had fear of addiction to corticosteroid treatment (5). According to Roncada and et al. (17), 40% of the parents observed to believe drug dependance to ICS. It was observed that the concern about ICS addiction may

originate from socio-cultural perceptions of inhaled drugs such as marijuana and heroin (7). In our study, 33% of the parents had fear of dependence to drugs.

It was observed that uncontrolled asthma have a negative effect on linear growth (18). In a study, children with asthma who have received long-term treatment with budesonide attain normal adult height (19). In our study, 27% of the parents had fear of growth retardation. Oral corticosteroids are known to reduce bone density and cause increasing in fracture risk in children, unlike this finding ICS on childrens' bone health has not observed yet (20). In studies, it was not observed that either ICS significantly reduce the bone mineral density, or increase the risk of fractures among children with asthma (21-24). In another study, it was observed that the risk of osteopenia and osteoporosis are neglible in patients receiving low to moderate dose of ICS (12). In our study, 16% of the parents had fear of bone weakness.

According to Boulet, misconception of reduction in efficacy of medication over time was observed in 38% of the patients. Although it is an expected condition to be seen in severe patients, it may also be in mild and moderate patients (4). In our study, 23% of the parents had fear of need for larger doses later on.

According to Rangachari and et al. (25), it was observed that parents who misunderstand the role of their childs' ICS medicine are less likely to report adherence to its' daily use. According to Boulet, most patients mentioned that they had not discussed their fears and concerns about ICS with their physician. After discussing with their physican, 75% of the patients stated that their concerns were eased (4). It was observed that parents' perspective of children with asthma affect the duration and dose of the ICS treatment they will give to their children and directly influence the level of asthma control. This perspective can be modified by partnership with physician (26). Therefore, talking to patients and informing them about their treatments and the possible side effects of these treatments will increase the confidence and compliance of patients and their caregivers with the treatment, and will provide significant benefits in symptom control of the patients. In addition to allocating sufficient time for anamnesis and physical examination at each visit, allocating time to issues that patients and parents fear and worry about the disease and/or its treatment, will increase the success of the treatment. Unlike these findings, in our study, patients who did not know the treatment of asthma, and not know the role of corticosteroid in asthma, tended not to have fear of corticosteroid treatment. However, it was observed that patients tended to use more irregulary in patients who did not know both the asthma treatment and the role of corticosteroid treatment in asthma.

CONCLUSION

In our study, 78% of the parents had fear and concern of potential adverse effects of inhaled corticosteroid treatment. The most common fear and concerns were about weight gain, dependance to drug, and growth retardation.

This study prompts that it is important to provide adequate information about disease and medication to the parents, and enlighten them about facts for easing concerns and fears of parents about side effects of corticosteroid treatment, improving adherence to treatment and improving outcomes of children' asthma control.

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Original Article

A Familiar Face in the Treatment of Immunoglobulin A Vasculitis: Colchicine

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ABSTRACT

Objective: The aim of the this study was to evaluate immunoglobulin A vasculitis (IgAV) patients on colchicine therapy and determine the causative factors leading to the initiation and maintenance of colchicine.

Material and Methods: This retrospective study was conducted receiving IgAV patients on colchicine at our clinic between January 2013 and June 2023. Demographic, clinical, and laboratory data of IgAV patients were obtained from their electronic medical records.

Results: A total of 33 IgAV patients receiving colchicine, 20 (60.6%) males and 13 (39.4%) females, were included in the study. The mean age at diagnosis of IgAV was 111.6±45.5 months. Colchicine was initiated in 13 (39.4%) patients with persistent rash, 8 (24.2%) with severe gastrointestinal tract involvement, seven (21.2%) with generalized/severe rash, and five (15.2%) with recurrent IgAV. The median elapsed time to colchicine initiation was 30 (10.5-60) days. The median duration of colchicine usage was ten (IQR, 6-54) months. Colchicine treatment was discontinued in 14 patients after a median 6.5 (IQR, 3-11.2) months. At the last visit, 13 (39.4%) patients were receiving colchicine for familial Mediterranean fever (FMF), four (12.1%) for recurrent IgAV, and two (6.1%) for persistent rash.

Conclusion: Colchicine should be kept in mind especially in the presence of severe, persistent or recurrent rash. Early initiation of colchicine treatment should be considered in IgAV patients with severe GI tract disease, especially in countries where FMF is common.

Key Words: Colchicine, Immunoglobulin A vasculitis, Leukocytoclastic vasculitis, Recurrence

INTRODUCTION

Immunoglobulin A vasculitis (IgAV; also known as Henoch-Schoenlein purpura), is a multisystemic disease characterized by cutaneous, gastrointestinal (GI) tract, articular, and renal involvement. Although IgAV is the most common vasculitis of childhood, its etiology and pathogenesis are still uncertain (1). Clinical manifestations are diagnostic, but sometimes skin biopsy may be required in the presence of atypical or persistent rash. The histopathological finding of IgAV is leukocytoclastic vasculitis (LCV) characterized by IgA deposition mostly in dermal capillaries and postcapillary venules (2). It is often a self-limiting disease. Sometimes severe and generalized skin rash, severe GI tract symptoms, or renal involvement may require pharmacological treatment. Corticosteroids are the first agent recommended for these patients. In patients

Conflict of Interest : On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics Committee Approval : This study was conducted in accordance with the Helsinki Declaration Principles. This study was approved by the Ankara Bilkent City Hospital Clinical Researches Ethics Committee (Date: 24/01/2024, Decision No: E2-24-6126).

Contribution of the Authors* : *POLAT M: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***IŞIKLAR EKİCİ M:*** Planning methodology to reach the conclusions. ***KAPLAN MM:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials. ***ÇELİKEL E:*** Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in patient follow-up. ***EKİCİ TEKİN Z:*** Taking responsibility in patient follow-up. ***GÜNGÖRER V:*** Taking responsibility in patient follow-up. ***KARAGÖL C:*** Taking responsibility in patient follow-up. ***ÖNER N:*** Collection of relevant biological materials, data management and reporting. ***ÖZTÜRK D:*** Collection of relevant biological materials, data management and reporting. ***ÖZÇELİK E:*** Collection of relevant biological materials, data management and reporting. ***UĞUR ES Y:*** Taking responsibility in necessary literature review for the study. ***YOĞUN SN:*** Taking responsibility in necessary literature review for the study. ***ÇELİKEL ACAR B:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar.

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with an inadequate response to corticosteroids or in organ- or life-threatening conditions, other immunosuppressive therapies such as intravenous immunoglobulin, cyclophosphamide, or mycophenolate mofetil (MMF) are suggested (3).

Colchicine is an alkaloid that acts its anti-inflammatory effects by binding to tubulin and disrupting microtubule assembly. In fact, inhibition of microtubule polymerization inhibits neutrophil chemotaxis and activity, reduces neutrophil-platelet interaction and aggregation, and consequently suppresses inflammation (4). Although colchicine is mainly used in the treatment of familial Mediterranean fever (FMF) and gout, it is also recommended in the management of LCV (5). In addition, the use of colchicine alone or in combination with dapsone is known to lead to prompt and complete resolution of persistent and/or recurrent cutaneous vasculitis (6).

In this study, we aimed to evaluate IgAV patients receiving colchicine therapy and determine the causative factors leading to the initiation and maintenance of colchicine.

MATERIALS and MERTHODS

Study design and participants

This study retrospectively analysed the electronic medical records of pediatric IgAV patients receiving colchicine who fulfilled the Ankara 2008 classification criteria at a tertiary referral hospital between January 2013 and June 2023. According to these criteria, petechiae or purpura with predominance in the lower extremities should be accompanied by at least one of the following four criteria: (1) IgA predominance on histopathology, (2) acute onset arthralgia/arthritis, (3) acute onset abdominal pain, (4) renal involvement. Patients diagnosed with any vasculitis, such as adenosine deaminase 2 deficiency or ANCA-associated vasculitis, and/or a connective tissue disease at presentation or during follow-up were excluded (7). During the study period, the electronic medical records of 54 IgAV patients receiving colchicine were evaluated. Eight patients, all with FMF, were excluded as they were receivingcolchicine treatment at the time of IgAV diagnosis. Our country is one of the regions where FMF is common. Since the association between FMF and IgAV is well known, all IgAV patients are evaluated for FMF symptoms in our clinic. MEFV mutation is performed in patients with a suspicious clinical history of FMF. Thirteen patients who fulfilled Yalçınkaya-Özen criteria or Eurofever classification criteria and therefore initiated colchicine were not included in the study (8,9). The remaining 33 patients were included in the study.

Demographic, clinical, and laboratory data were obtained from the electronic medical records. Age at diagnosis, gender, follow-up period, systemic involvements, and treatment modalities were analyzed. The time of colchicine initiation, duration of usage, and causative factors for initiation and continuation were recorded. MEFV gene analysis were noted. Histopathological features of skin biopsy were analyzed with hematoxylin-eosin staining and direct immunofluorescence.

Persistence of active purpuric or petechial rash after the first month of IgAV diagnosis was defined as persistent rash. General/severe rash was defined as rash above the waist or necrotic or bullous rash.

Severe GI tract involvement was defined as massive GI tract bleeding, refractory ongoing abdominal pain despite receiving corticosteroid, or severe abdominal complications such as intestinal perforation or obstruction, intussusception, and hypovolemic shock.

Recurrence was defined as a new flare of symptoms attributable to IgAV in a patient previously diagnosed with IgAV after a symptom-free period of at least one month.

Disease activity was assessed using the pediatric vasculitis activity score (PVAS) based on the evaluation of the following nine organ systems: general, skin, mucous membranes/eyes, ear/nose/throat, cardiovascular, respiratory, GI tract, renal, and nervous systems (10).

This study was approved by the Ankara Bilkent City Hospital Clinical Researches Ethics Committee (Date: 24/01/2024, Decision No: E2-24-6126). All procedures were performed in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Statistical analyses

Statistical analyses were performed using the IBM Statistical Package for the Social Sciences, version 25.0 (SPSS Inc., Armonk, NY, IBM Corp., USA). Descriptive analyses were presented using means and standard deviations for normally distributed variables, medians and interquartile range for the non-normally distributed and ordinal variables, and frequencies for the categorical variables.

RESULTS

A total of 33 IgAV patients receiving colchicine, 20 (60.6%) males and 13 (39.4%) females, were included in the study. The mean age at diagnosis of IgAV was 111.63±45.52 months. Rash was present in all patients at presentation. Twenty-nine patients (87.9%) had purpura, two (6.1%) had bullous rash and the other two (6.1%) had necrotic rash. The rash was localized on the lower extremities and buttocks in 17 patients (51.5%). In ten (30.3 %) patients, rash was also present in the upper extremities and trunk. The remaining 6 (18.2%) patients had rash all over the body including the face. In addition, subcutaneous edema was present in 14 (42.4%) patients. Following skin involvement, the GI tract was the most commonly involved system (63.6%), followed by articular (33.3%), renal (18.2%), and scrotal (9.1%) involvement, respectively.

MEFV mutation was performed in all patients except two (6.1%). Eleven (33.3%) patients had no mutation, while 18 (54.5%) had at least one exon 10 mutation. FMF symptoms occurred in 13 (72.2%) of 18 patients with exon 10 mutation during follow-up, and colchicine was continued.

Skin biopsy was performed in 5 (15.2%) patients with persistent rash, 3 (9.1%) with recurrent IgAV, and 2 (6.1%) with generalized/severe skin involvement. Findings of skin biopsy were consistent with LCV with IgA deposits.

Table I: Demographic and clinical characteristics of immunoglobulin A vasculitis patients receiving colchicine

	IgAV patients receiving colchicine (n=33)
Gender, Male*	20 (60.6)
Age at diagnosis (months)†	111.6±45.5
Follow-up time (months)‡	24 (8-60)
Colchicine initiation time (days)‡	30 (10.5-60)
Duration of colchicine use (months)‡	10 (6-54)
System involvement*	
Cutaneous	33 (100)
Rash	33 (100)
Subcutaneous edema	14 (42.4)
Articular	11 (33.3)
Gastrointestinal tract	21 (63.6)
Renal	6 (18.2)
Scrotal	3 (9.1)
Rash distribution*	
Lower extremities and buttocks	17 (51.5)
Upper extremities or trunk	10 (30.3)
Involve face	6 (18.2)
Rash characteristic*	
Purpura	29 (87.9)
Bullous	2 (6.1)
Necrotic	2 (6.1)
MEFV*	
None	2 (6.1)
Negative	11 (33.3)
Positive	
Exon 10 homozygous	2 (6.1)
Exon 10 heterozygous	12 (36.4)
Exon 10/ Exon 10; compound heterozygous	3 (9.1)
Exon 10/ Not Exon 10; compound heterozygous	1 (3)
Other	2 (6.1)
Treatment*	
Corticosteroid (2 mg/kg/day)	29 (80.4)
Pulse methylprednisolone (30 mg/kg/day)	12 (36.4)
Intravenous immunoglobulin	2 (6.1)
Cyclophosphamide	6 (18.2)
Plasmapheresis	1 (3)
Recurrence*	7 (21.2)
Cutaneous	4 (12.1)
Cutaneous + Gastrointestinal tract	2 (6.1)
Cutaneous + Scrotal	1 (3)
Elapsed time until recurrence‡	12 (5-48)
PVAS at the time of diagnosis‡	2 (2-3)

:** *n(%),* **†:** *mean±SD,* **‡:** *median (Interquartile range),* ***IgAV: *Immunoglobulin A vasculitis,* ***PVAS:*** *Pediatric Vasculitis Activity Score*

Before initiation of colchicine, three (9.1%) patients had not received any treatment except nonsteroidal anti-inflammatory drugs. Seventeen (51.5%) patients received corticosteroids for GI tract involvement, seven (21.2%) for skin involvement, four (12.1%) for GI tract + renal involvement, and two (6.1%) for renal involvement. Immunosuppressive treatment was given to eight (24.2%) patients, and plasmapheresis was performed in one (3%) patient with severe GI tract involvement refractory to steroid treatment. Seven (21.2%) patients developed recurrence a median 12 (IQR, 5-48) months after the first IgAV diagnosis. Median PVAS was two (IQR, 2-3) points at the time of diagnosis. Demographic, clinical and laboratory characteristics of IgAV patients receiving colchicine are given in Table I.

Colchicine was initiated in 13 (39.4%) patients with persistent rash, eight (24.2%) with severe GI tract involvement, seven (21.2%) with generalized / severe rash, and five (15.2%) with recurrent IgAV. The median elapsed time to colchicine initiation was 30 (10.5-60) days. The median duration of colchicine usage was ten (IQR, 6-54) months. Colchicine was initiated in a total of 20 (60.6%) patients owing to severe or persistent rash. The rash resolved completely with colchicine in all patients except one (3%). This patient was a 16-year-old girl with persistent and generalized rash. MMF was initiated in the 4th month of colchicine treatment as her rash still persisted. She recovered almost completely in the 1st month of MMF treatment. No recurrence was observed after colchicine in any of the patients who were initiated on colchicine due to recurrent IgAV. Colchicine treatment was discontinued in 14 patients after a median 6.5 (IQR, 3-11.2) months. During follow-up, 13 (39.4%) patients were diagnosed with FMF and continued colchicine treatment. Among these patients, seven (21.2%) were receiving colchicine for severe GI tract involvement, three (6.5%) for persistent rash, two (6.1%) for recurrent IgAV and one (3%) for generalized/severe rash. In addition, colchicine was continued in four (12.1%) patients due to recurrent LCV and in two (6.1%) due to persistent rash (Figure 1). The mean duration of colchicine usage was 17.5±12.55 months in patients with recurrent LCV and 7±1.41 months in patients with persistent rash.

DISCUSSION

Immunoglobulin A vasculitis is usually self-limiting, but intensive immunosuppressive therapies may be required in severe organ involvement. The first and most preferred agent is corticosteroids and occasionally other cytotoxic agents may be needed (11). Some patients may not respond to corticosteroids in cases such as severe and generalized rash or recurrent IgAV. Colchicine is an anti-inflammatory drug with a tolerable side effect profile that has been used for years in the treatment of various vasculitides. In this study, it was shown that colchicine treatment was effective in a small group of patients.

Skin manifestations, which are mandatory classification criteria in IgAV, are usually limited to the lower extremities and resolve spontaneously. However, approximately 2% of patients may have a generalized rash, or severe rash with bullous or necrotic characteristics (11,12). Severe cutaneous manifestations are known to be associated with the risk of developing severe GI tract complications and nephritis (13,14). Moreover, necrotic and dehisced bullous lesions may result in infections. Apart from these life- and organ-threatening complications, severe skin lesions may cause social and cosmetic anxiety in patients and their families. In fact, Sestan et al. (13) reported that about half of IgAV patients with severe cutaneous manifestations had permanent skin sequelae (post inflammatory hyperpigmentation or permanent scars). The optimal treatment of IgAV patients with severe cutaneous involvement is still unknown. Corticosteroids are

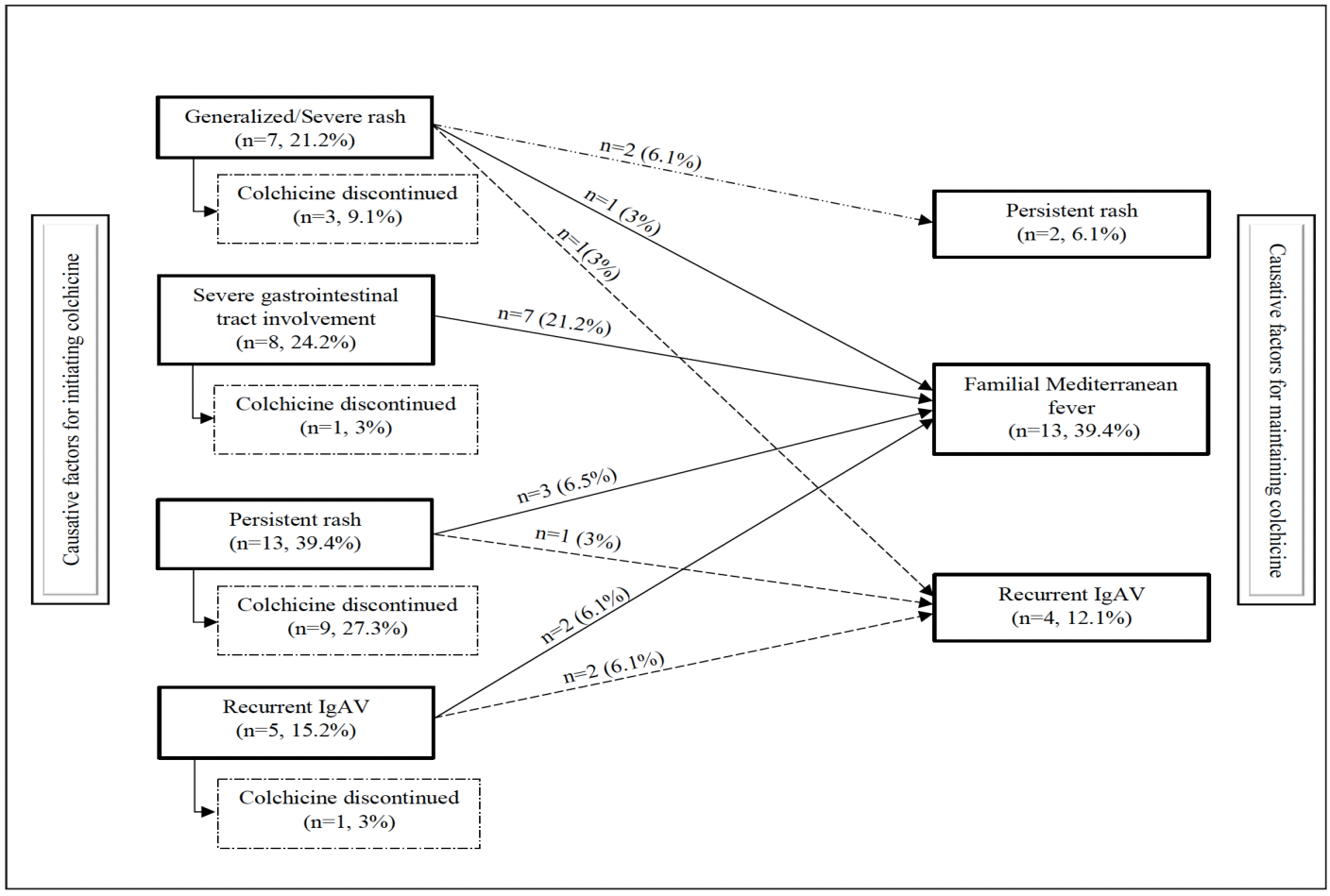

Figure 1: Flowchart showing the reasons for initiating and maintaining colchicine in IgAV patients. **IgAV:** Immunoglobulin A vasculiti

usually the first-line drug of choice for the treatment of severe skin lesions. There are also studies reporting that early corticosteroid treatment reduces scar formation by providing faster resolution of skin symptoms (11,13,15). Similarly, in our study, patients with severe skin involvement received corticosteroid treatment most frequently. However, considering the side effects that may occur with long-term use of corticosteroid therapy, early initiation of steroid-sparing agents is logical. LCV is a small vessel vasculitis histologically characterized by neutrophilic infiltration and nuclear debris around postcapillary venules, fibrin deposits in the vessel wall, and erythrocyte extravasation (16). Considering that colchicine acts its anti-inflammatory effects through neutrophils, it can be predicted that it may be effective in the treatment of LCV. Although there are no randomized studies showing the efficacy of colchicine in pediatric IgAV patients, it has been reported to be an effective treatment option in various case reports (17-19). However, the time of initiation and duration of colchicine use are still unanswered questions. In our study, colchicine treatment was used successfully in patients with severe or persistent skin rash. Nevertheless, all of these patients had received corticosteroids or nonsteroidal anti-inflammatory drugs as previously reported in the literature. Colchicine treatment is beneficial in some cases, as demonstrated by the long-term follow-up of our study, including the period after other immunosuppressives were discontinued.

In IgAV, if there is a concomitant rheumatologic disease and/or uncontrolled inflammation secondary to any disease, the disease course is likely to be more severe than expected or relapse may occur. FMF is the most common autoinflammatory disease caused by gain-of-function mutations in the MEFV gene. Some studies have reported that the presence of MEFV mutations in IgAV patients may be responsible for high inflammation and poor clinical outcome (20, 21). In these studies, it was also reported that GI tract involvement was more severe in the presence of MEFV mutation variant in exon 10. In our study, colchicine treatment was also initiated in egiht patients with severe GI tract involvement to suppress inflammation in the acute period. Exon 10 mutation was found in seven patients, and they continued colchicine treatment for FMF.

The main limitation of this study is that it was conducted retrospectively from a single center. However, given that there are only a few case reports of colchicine experience in pediatric IgAV patients, we believe that this largest pediatric cohort data will be informative for clinicians.

CONCLUSION

Although IgAV patients respond well to supportive care or short-term corticosteroid use, colchicine treatment should be kept in mind especially in the presence of severe, persistent or recurrent

rash. In addition, early initiation of colchicine treatment should be considered in IgAV patients with severe GI tract disease, especially in countries where FMF is common.

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Original Article

Ambulatory Blood Pressure Monitoring in Children: Single Center Experience

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ABSTRACT

Objective: Ambulatory blood pressure monitoring (ABPM) is the preferred method for diagnosis of hypertension(HT) in children. Here, we aimed to demonstrate the reasons for ABPM application and incidence of HT, white coat and masked HT in our cohort besides the evaluation of dipping status, biochemical and radiological parameters between the patients with normotension, elevated blood pressure(EBP) and HT.

Material and Methods: Twenty-four hour ABPM results of children followed at department of pediatric nephrology and whose office blood pressure measurements revealed HT or EBP and ABPM records of normotensive patients having chronic kidney disease or renal anomalies were evaluated retrospectively. Twenty-four hour ABPM SD score ≥1.96 defined HT while the value between 1.64 and 1.95 indicated EBP. In addition to assessment of blood pressure loads and nocturnal dipping; age, gender, body mass index(BMI), proteinuria, kidney function tests and ultrasound of urinary system were also assessed.

Results: Although ABPM was applied to total of 244 patients, 189 of them were included in the study. High casual blood pressure measurements in 108 (57.1%) asymptomatic patients constituted the major group for ABPM application. Total of 57 patients (30.2%) were normotensive, 18 (9.5%) with EBP and 114 (60.3%) were hypertensive. No difference was found in regards of BMI, proteinuria, serum creatinine levels and sonographic results between the groups. Patients with HT and EBP had significantly lower nocturnal dip than normotensive group ($p<0.001$). However there was no difference in number of patients with inadequate nocturnal fall in all three groups.

Conclusion: ABPM should be preferred for definitive diagnosis of HT in childhood. Patients with inadequate nocturnal fall should be evaluated carefully and followed-up regularly as it had been implicated in the development of cardiovascular disease.

Key Words: Ambulatory blood pressure, Childhood, Hypertension, Nocturnal dipping

INTRODUCTION

Accurate measurement and evaluation of blood pressure (BP) are initial steps for definitive diagnosis of hypertension (HT) in children and adults. After HT has been detected, it should be investigated for underlying pathology and then a management protocol should be planned promptly to prevent cardiovascular complications. Ambulatory blood pressure monitoring (ABPM) is the preferred method over office BP measurements in children as it's considered to reduce environmental and anxiety-related measurement errors. ABPM parameters have also been shown to have a closer relationship with target organ damage (TOD) such as left ventricular

Conflict of Interest : On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics Committee Approval : This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Kocaeli University, Faculty of Medicine Ethics Committee (09.05.2023-2023/111).

Contribution of the Authors* : *AYTAÇ MB: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***DOĞAN K:*** Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***ERGÜL ŞA:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***MALKOÇ ND:*** Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***BEK K:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, Reviewing the article before submission scientifically besides spelling and grammar

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hypertrophy (LVH), increased carotid intima-media thickness (cIMT) and arterial stiffness (1,2).

So far, ABPM with continuous readings during 24-hour period, has provided significant clinical data about masked hypertension, BP load and isolated nocturnal HT especially in patients with chronic kidney disease, obesity or diabetes (3). ABPM is also a diagnostic tool for identification of white coat hypertension (WCH) defined as high office BP with ambulatory normotension which is considered to be a pre-hypertensive state in adult studies while any risk has not been reported yet to be correlated with TOD in children (4-6).

The aims of the present study are: (a) to investigate the reasons of ABPM application in children, (b) to determine the incidence of HT, elevated BP (EBP), WCH and MH in our cohort, (c) to assess the frequency of nocturnal dipping status, and (d) to compare the anthropometric, biochemical and radiological parameters between children with normotension, EBP and HT.

MATERIALS and METHODS

In this retrospective study, 24-hour ABPM records of the patients between the ages of 5 and 18-years-old with a height of >120 cm who had been followed up by the department of pediatric nephrology at Kocaeli University School of Medicine from February 2020 to October 2022, were investigated. ABPM had been applied to the children with EBP or HT on office measurements; and also it had been used to screen nocturnal HT in children having chronic kidney disease and congenital renal anomalies with normal office BP. The charts of each patient were reviewed for age, gender, anthropometric data and pastmedical history. Presence of proteinuria, kidney function tests and urinary Doppler ultrasound results were also assessed. The study was approved by Kocaeli University, Faculty of Medicine Ethics Committee (09.05.2023-2023/111). The study was performed in accordance with the Declaration of Helsinki.

Reference values were used to calculate SD scores for weight and height (7). Body mass index (BMI) was defined as the weight (kg) divided by height squared (m^2).

Serum creatinine, urea and blood urea nitrogen (BUN) were measured on the same day of ABPM. Protein to creatinine ratio (mg/mg) in spot fresh morning urine was used. Renal lengths were determined with ultrasound performed within 3 months and SD scores of renal lengths were calculated according to previously reported data (8).

Office BP was measured with an automated oscillometric device (Lutech Datalys 808, USA) after 5 minutes of rest using appropriate sized cuff for each patient. EBP was defined as systolic and/or diastolic office BP between 90th and 95th percentile whereas values above the 95th percentile was considered as hypertension based on recently published American Academy of Pediatrics guideline (9).

All subjects with EBP and HT on office measurements underwent 24-h ABPM. It was performed with an oscillometric device (Mobil-O-Graph, IEM GmbH, Stolberg, Germany) and proper sized cuff on the non-dominant arm. BP was measured every 15 minutes during the daytime and every 30 minutes at night. Subjects were instructed to keep their arm relaxed while it was measuring and were encouraged to maintain their usual activities. They were asked to avoid strenuous exercise and sleeping during the day. Sleep at night and wake times were requested to be noted. Regarding the young age of patients, only recordings with 70% of the expected number of readings were included for the study.

Twenty-four hour ABPM SD scores based on gender and height were calculated for mean systolic, diastolic BP and mean arterial pressure (MAP) using the normative data of healthy children (10). Twenty-four hour ABPM SD score ≥ 1.96 defined hypertension whereas ≥ 1.64 but<1.96 score revealed EBP. Systolic and diastolic BP load (%) indicates the proportion of measurements above the 95th percentile reference adjusted for gender and height. Systolic and diastolic dipping status (%) were calculated as mean daytime BP minus mean sleeping BP divided by mean daytime BP. Inadequate nocturnal dipping was described as a drop of less than 10%.

Office BP above 95th percentile but mean ABPM SDS<1.96 with BP load <25% was described as WCH. Office BP below 95thpercentile but mean ABPM SDS>1.96 with BP load>25% was diagnosed as MH (11).

Statistical analysis

Continuous variables are expressed as mean and standart deviation in normal distribution and as median and interquartile range in non-normal distributed cases. Student's t test or Mann-Whitney U test were used to analyze the differences between groups; one-way ANOVA or Kruskal-Wallis for the comparison of multiple categories. Qualitative variables were compared using Chi-square test. IBM Statistical Package for the Social Sciences, version 22.0 (SPSS Inc., Armonk, NY, IBM Corp., USA)22 statistical software was used for analysis and p value of 0.05 or lower was considered significant.

RESULTS

A total of 244 patients underwent 24-h ABPM between February 2020 and October 2022. In cases of multiple practices, only the first successful 24-h study was used and the subjects with

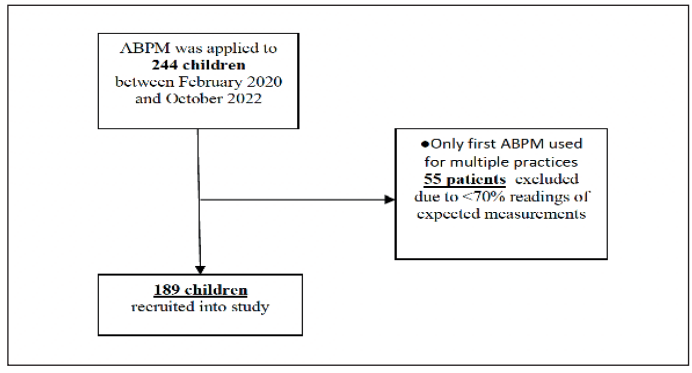

Figure 1: Inclusion criteria for the study. ABPM ambulatory blood pressure monitoring

Table I: Patient characteristics

	Normal (n=57)	EBP (n=18)	HT (n=114)	p
Age(years)*	14.4 (10.33-15.79)	12.78 (9.8-14.97)	14.95 (12.47-16.16)	0.040‖
Male(%)†	31 (54.4)	9 (50)	67 (58.8)	0.710‖
Height (cm)*	162 (137-173)	153.5 (135-172.2)	165 (151-173)	0.240‖
Height SD score‡	0.31 ± 1.08	0.16 ± 1	0.09 ± 1.14	0.480§
Weight (kg)‡	63.05 ± 27.8	55.05 ± 23.63	64.35 ± 22.76	0.320§
Weight SD score*	1.34 (0.3-2.2)	1.14 (0.04-1.53)	1.18 (0.55-1.92)	0.480‖
BMI ‡	24.42 ± 6.54	22.15 ± 4.97	24.6 ± 5.52	0.240§
BMI SD score*	1.42 (0.48-1.97)	0.99 (0.11-1.71)	1.34 (0.35-1.98)	0.500‖
Renal parameters*				
Serum creatinine(mg/dl)	0.59 (0.47-0.68)	0.55 (0.47-0.73)	0.64 (0.53-0.79)	0.430‖
Urine protein/creatinine(mg/mg)	0.14 (0.1-0.2)	0.14 (0.1-0.23)	0.13 (0.09-0.21)	0.700‖
Renal lenght(mm)				
Right	95 (86.5-96.5)	91 (81-111.25)	94 (89.75-100)	0.800‖
Left	98 (88.5-105)	98.5 (85-125.75)	99 (93-104)	0.360‖
Renal lenght SD score				
Right	-1.16 (-2.11- -0.15)	-1.13 (-1.68-1.24)	-1.12 (-2.1-0.01)	0.620‖
Left	-0.54 (-0.83-0.33)	-0.17 (-0.93-2.78)	-0.46 (-1.28-0.31)	0.210‖

:** *median (interquartile range),* **†:** *n(%),* **‡:** *mean ± standart deviation,* **§:** *one-way ANOVA Test,* **‖:** *Kruskal-Wallis Test,* ***EBP: *Elevated blood pressure,* ***HT:*** *Hypertension,* ***SD:*** *Standard deviation,* ***BMI:*** *Body mass index*

Table II: Ambulatory BP data

	Normal (n=57)	EBP (n=18)	HT (n=114)	p
24-h values				
24-h systolic BP (mmHg)*	113.54 ± 6.54	115.83 ± 5.38	123.14 ± 8.21	<0.001‡
24-h systolic BP SD score*	0.05 ± 0.54	0.51 ± 0.44	1.2 ± 0.97	<0.001‡
24-h diastolic BP (mmHg)*	61.82 ± 4.85	65.5 ± 3.51	71.56 ± 6.66	<0.001‡
24-h diastolic BP SD score*	-1.03 ± 0.94	-0.29 ± 0.67	0.72 ± 1.17	<0.001‡
24-h MAP (mmHg)*	85 (82-89)	87.5 (86-91)	95 (92-98)	<0.001‡
24-h MAP SD score*	0.62 ± 0.54	1.26 ± 0.37	2.28 ± 1.07	<0.001‡
Day systolic BP (mmHg)*	116.37 ± 7.15	118.06 ± 6.18	125.09 ± 9.21	<0.001‡
Day systolic BP SD score*	-0.21 ± 0.57	0.12 ± 0.4	0.74 ± 0.99	<0.001‡
Day diastolic BP (mmHg)*	64.19 ± 5.04	67.39 ± 4.03	73.11 ± 7.62	<0.001‡
Day diastolic BP SD score*	-1.36 ± 0.78	-0.83 ± 0.71	0.12 ± 1.24	<0.001‡
Day MAP (mmHg)*	88.09 ± 5.21	90.61 ± 4.24	96.86 ± 7.03	<0.001‡
Day MAP SD score*	0.22 ± 0.6	0.66 ± 0.4	1.6 ± 1.11	<0.001‡
Night systolic BP (mmHg)†	105 (101-108.5)	109.5 (106.75-111)	116 (112-120)	<0.001§
Night systolic BP SD score†	0.49 (-0.05-0.78)	0.95 (0.38-1.46)	1.65 (1.05-2.24)	<0.001§
Night diastolic BP (mmHg)†	55 (51.5-57)	59 (58-61)	65 (62-68.25)	<0.001§
Night diastolic BP SD score†	-0.13 (-0.79-0.28)	0.55 (0.31-0.76)	1.45 (0.93-1.98)	<0.001§
Night MAP (mmHg)†	78 (74-80)	82 (80.75-83)	88 (86-91)	<0.001§
Night MAP SD score†	1.14 (0.78-1.34)	1.81 (1.71-1.87)	2.66 (2.23-3.38)	<0.001§
BP load and dipping†				
Day systolic BP load (%)	20 (12.5-36)	22.5 (18.75-45)	39 (21-55.5)	<0.001§
Day diastolic BP load (%)	9 (2.5-15.5)	16.5 (10.25-20.25)	23.5 (10-50)	<0.001§
Night systolic BP load (%)	21 (11.5-47)	36 (16.25-69)	57 (32-82.7)	<0.001§
Night diastolic BP load (%)	0 (0.0-7.5)	11 (5.75- 22.25)	22 (8.75-46)	<0.001§
Systolic BP dipping (%)	9.4 (6.8-13.05)	7.7 (5.17-9.5)	5.9 (3.17-11.15)	<0.001§
Diastolic BP dipping (%)	15.9 (9.75-19.05)	13.2 (6.3-16.02)	10.15 (3.25-15.92)	<0.001§

:** *mean ± standart deviation,* **†:** *median (interquartile range),* **‡:** *one-way ANOVA Test,* **§:** *Kruskal-Wallis Test,* ***EBP: *Elevated blood pressure,* ***HT:*** *Hypertension,* ***SD:*** *Standard deviation,* ***BP:*** *Blood pressure,* ***MAP:*** *Mean arterial pressure*

available readings of at least 70% of the expected measurements were included in the study. Eventually, the study sample consisted of 189 patients (Figure 1). One hundred and seven (56.60%) of them are male. The mean age was 13.65±3.14 years.

The main indication for ABPM was consisted of 108 (57.10%) asymptomatic patients with high office BP (>90th percentile) according to the recent published guidelines (9). Symptomatic children having high office BP presented with headache in 62 (32.81%) patients, dizziness in six, chest pain in two, palpitations in two and syncope in one patient.

Of the asymptomatic 108 patients, EBP was found in nine (8.32%) and hypertension in 64 (59.20%) patients. Of the 62 children who underwent ABPM due to headache, five patients (8%) had EBP and 41 (66.11%) had HT.

Table III: BP load and dipping status in patients

	Normal (n=57)	EBP (n=18)	HT (n=114)	p†
Day systolic BP load*				
<25%	33 (57.9)	10 (55.6)	37 (32.5)	0.003
≥25%	24 (42.1)	8(44.4)	77 (67.5)	
Day diastolic BP load*				
<25%	52 (91.2)	16 (88.9)	57 (50)	<0.001
≥25%	5 (8.8%)	2 (11.1)	57 (50)	
Night systolic BP load*				
<25%	31 (54.4)	7 (38.9)	17 (14.9)	<0.001
≥25%	26 (45.6)	11 (61.1)	97 (85.1)	
Night diastolic BP load*				
<25%	56 (98.2)	14 (77.8)	59 (51.8)	<0.001
≥25%	1 (1.8)	4 (22.2)[b]	55 (48.2)	
Systolic BP dipping*				
<10%	31 (54.4)	14 (77.8)	80 (70.2)	0.066
≥10%	26 (45.6%)	4 (22.2)	34 (29.8)	
Diastolic BP dipping*				
<10%	15 (26.3)	7 (38.9)	57 (50)	0.011
≥10%	42 (73.7)	11 (61.1)	57 (50)	

:** *n (%),* **†:** *Chi-square Test,* ***BP: *Blood pressure,* ***EBP:*** *Elevated blood pressure,* ***HT:*** *Hypertension,* ***SD:*** *Standard deviation*

Among 189 subjects, 57 (30.20%) were normotensive, 18 (9.50%) had EBP and 114 (60.30%) were classified as hypertensive based on ABPM SD scores. Gender, height, weight and BMI SD scores were not different between these groups. No statistically significant difference was found among the groups in terms of proteinuria, serum creatinine level, renal length SD scores and findings of doppler ultrasound (Table I).

Systolic and diastolic nocturnal dipping were significantly lower in patients with HT when compared to EBP and normotensive group [(5.90% (3.17-11.15) vs 7.70% (5.17-9.50) and 9.40% (6.80-13.05) p<0.001 for systole, 10.15% (3.25-15.94) vs 13.20% (6.30-16.02) and 15.90% (9.75-19.05) p<0.001 for diastole, respectively)]. ABPM SD scores, BP load and dipping status were presented in Table II. Nevertheless; the incidence of having inadequate systolic nocturnal dip was not statistically different between normotensive, EBP and hypertensive groups (Table III).

Among 57 patients in whom hypertension was not detected according to ABPM measurements, there were three patients with autosomal dominant polycystic kidney disease (ADPKD), one with familial mediterrenian fever (FMF), one autosomal recessive polycystic kidney disease (ARPKD), one Williams Syndrome, one Alport Syndrome, one nephrotic syndrome, one ureteropelvic junction (UPJ) obstruction and one patient with double renal artery. Of the remaining 47 healthy children; 11 (23.40%) had both systolic and diastolic nocturnal nondipping, 11 (23.40%) had only systolic nondipping and two patients (4.20%) were found to have nocturnal nondipping only in diastole. Thirteen of these 47 children (27.60%) were asymptomatic and underwent on ABPM due to high office BP measurements.

Of the 114 patients whose diagnosis of hypertension was clarified based on ABPM SD scores; four patients had ADPKD, four had chronic kidney disease (CKD), three had double renal artery, three FMF, two UPJ obstruction, two neurogenic bladder, one coarctation of aorta, one neurofibromatosis, one renal artery stenosis, one horseshoe kidney, one Williams Syndrome, one systemic lupus erythematosus and one patient had ureterovesical junction obstruction. In the remaining 88 subjects, the ratio of having both systolic and diastolic nocturnal nondipping was 46.60% (41 patients), systolic nondipping was 26.10% (23 patients) and diastolic nondipping was 3.40% (three patients).

In the present study, the incidence of masked and white coat HT was 1.05% (two patients) and 11.11% (21 patients), respectively.

DISCUSSION

Although the effective role of ABPM for predicting cardiovascular complications in adults has been previously demonstrated, comparative studies including pediatric data are scarce due to low incidence of mortality and cardiovascular events in children. There have been limited pediatric reports indicating that high BP and BP load cause LVH and increased cIMT (12-15). In a study of 77 patients aged five to 19 years, 27 of whom were classified as non dippers; Bakhoum et al. (16) reported that they have developed more significant LVH than dippers. Moreover; obesity, obstructive sleep apnea, proteinuria and CKD have been described to be associated with blunted nocturnal dipping.

In a retrospective study including 408 subjects aged 5-21 years; Macumber et al. (17) have reported that both systolic and diastolic dipping were significantly blunted in obese group. Although the patients with CKD, congenital heart disease, prematurity, sleep disorders and medication use were not included in their study, the incidence of nocturnal non dipping was approximately 14% in 22 of 161 non-obese patients (17). In our overall study group, systolic and diastolic non dipping were calculated as 66.10% and 41.71% respectively. Although no statistical significant difference was detected leading to blunted nocturnal dip, the frequency of systolic nondipping was similar between patients with normotension, EBP

and hypertension. Moreover, abnormal nocturnal dip in systolic or diastolic blood pressure was found in 51% of 47 patients, who were classified as normotensive according to ABPM results and who did not have any underlying disease. This rate was also higher when compared to the report by Seeman et al. (18) revealing 30% nocturnal nondipping in 20 normotensive patients.

Some previous studies have revealed that nocturnal dipping status was not found to be significantly associated with LVH (19). Conversely; Szyszka et al. (20) has demonstrated higher LVMI in 50 non dipper patients when compared to 33 dipper patients. In adults, abnormal dipping status was associated with worsening kidney functions, development of CKD and increased cardiovascular morbidity (21-24). Although cardiac assessment could not be performed in the present study due to its retrospective design, it is crucial to evaluate and follow the patients with nocturnal non dipping despite being normotensive on ABPM, considering the previously reported consequences of inadequate nocturnal blood pressure fall on cardiovascular functions.

In spite of the low prevalence of WCH (0.60-1.20%) in the general pediatric population, it has been reported to be higher especially in patients referred for high office BP evaluation. In one study conducted in patients between the ages of 10 and 17 years; 54 of 174 (31%) patients had been diagnosed as having WCH, whereas another cohort with a mean age of 13.3 years has revealed its frequency as 52% (25-27). Inconsistently; we found a lower incidence of WCH in our patient groups. We also detected a lower frequency of masked hypertension; which has been demonstrated to have close relationship with increased cardiovascular morbidity (25-30). The fact that it has been usually associated with chronic kidney disease, obesity or coarctation of aorta; low number of patients having such an underlying disease might have been the reason for low MH ratio in the study sample.

The limitations of our study are the small number of patients with CKD or renal anomalies and the lack of assessments like cIMT and LVMI predicting the development of cardiovascular disease in the study protocol due to its retrospective design.

In conclusion, ABPM is now the most preferred method for correct diagnosis of childhood HT. The increasing frequency of hypertension in pediatric population should not be ignored particularly in healthy adolescents. To prevent the development of cardiovascular and renal diseases especially in non dippers; the diagnosis should be clarified by attaching ABPM for high office BP measurements under optimal environmental conditions and with appropriate cuff size.

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Case Report

Mycoplasma Pneumoniae Induced Rash and Mucositis (MIRM) in the Differential Diagnosis of Drug Allergy

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ABSTRACT

Mucocutaneous eruptions associated with *Mycoplasma pneumoniae* (MP) infection has been newly termed 'MP-induced rash and mucositis (MIRM)'. A 17-year-old male developed a rash, bilateral purulent conjunctivitis, and oral and genital ulcers after the first dose of amoxicillin-clavulanic acid, initially considered as a drug allergy. Following hospitalization under a preliminary diagnosis of Stevens-Johnson syndrome and initiation of systemic steroids, he developed pneumonia. Laboratory tests confirmed MP infection, leading to a refined diagnosis of MIRM. The patient fully recovered within two weeks following treatment with azithromycin and intravenous immunoglobulin. This case underscores the importance of considering MIRM in the differential diagnosis of drug allergies and aims to enhance awareness of this condition.

Key Words: Adolescent, Drug allergy, Mucositis, *Mycoplasma pneumoniae*, Rash

INTRODUCTION

Mycoplasma pneumoniae (MP) is a common respiratory pathogen that causes community-acquired pneumonia (CAP), occurring more frequently in children than in adults (1). Although most MP infections are typically mild, about 25% of patients may develop severe extrapulmonary complications, such as mucocutaneous blistering (2). Mucocutaneous eruptions associated with MP infection exhibit a wide range of morphological variations (3). Therefore, previously these eruptions have been categorized within the spectrum of erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) due to their multifaceted nature (3). Canavan et al. (3) initially described a new term as MP induced rash and mucositis (MIRM) and proposed diagnostic criteria. In this report, we present a case of an adolescent initially suspected of having a drug allergy, who was ultimately diagnosed with severe MIRM.

CASE REPORTS

A previously healthy 17-year-old boy was prescribed oral amoxicillin-clavulanic acid one week ago for fever and cough. One hour after the first dose of the drug, he developed a rash over his entire body. On the second day, he experienced redness, burning sensation, light sensitivity in the eyes, and the formation of fluid-filled blisters in the mouth. On the fourth day of taking the drug, as his symptoms persisted, he presented to our clinic with a suspected amoxicillin-clavulanic acid allergy. He had widespread ulceration of the oral mucosa, swollen eyelids and bilateral purulent conjunctivitis (Figure 1A-1B). Target-like lesions that did not tend to coalesce were observed on the extremities, anterior surface of the trunk, and back (Figure 1C, 1D). Ulcerative lesions were present on the glans penis and suprapubic region. There were no fever, lymphadenopathy, or organomegaly. Complete blood count revealed a white blood cell count of 11.700/mm^3, hemoglobin concentration

Conflict of Interest : *On behalf of all authors, the corresponding author states that there is no conflict of interest.*

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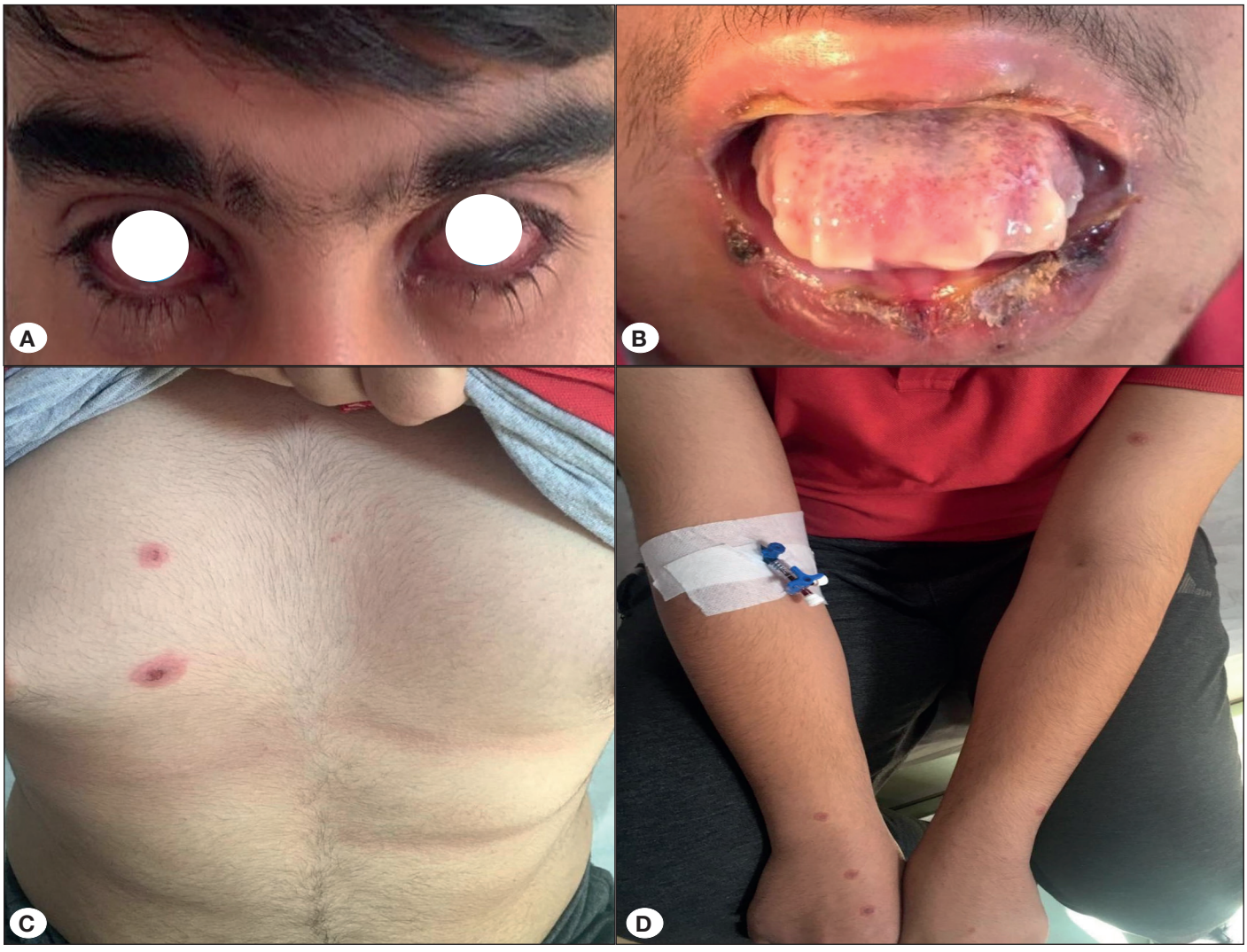

Figure 1: A) Due to MIRM bilateral purulent conjonctivitis, **B)** Due to MIRM ulceration of the oral mucosa, **C,D)** Due to MIRM targetoid lesions of the trunk and extremity

of 13 g/dL, platelet count of 405.000/mm^3, and CRP level of 172 mg/L (N: 0-5). Liver and kidney function tests were normal. The patient was admitted with a preliminary diagnosis of Stevens-Johnson syndrome. Treatment was initiated with intravenous methylprednisolone at a dose of 60 mg/day. Ophthalmology started treatment for ocular involvement including dexamethasone, bacitracin, moxifloxacin eye drops, and artificial tears. A symblepharon ring was placed. Urology inserted a urethral catheter due to genital involvement. Intravenous hydration and high-calorie formula were initiated for the patient with inadequate oral intake. On the 5th day of hospitalization, the patient required supplemental oxygen and bilateral crackles were heard at the lung bases. Serum *Mycoplasma pneumoniae* IgM were found to be positive. The PCR test performed on the nasopharyngeal specimen was positive for MP. Based on these findings, the patient was diagnosed with MIRM. The patient received a 5-day course of azithromycin treatment and a total of 400 mg/kg of intravenous immunoglobulin (IVIG) divided over 5 days. On the 2nd day of azithromycin therapy, the patient's oxygen requirement decreased. By the 14th day, regression of skin lesions was observed; methylprednisolone was gradually tapered off, and the patient was discharged. The patient has been consistently monitored without any complications for a period of three years. Written informed consent was obtained from the parents of the patient for publication.

DISCUSSION

Here, we report a case initially consulted for a suspected drug allergy and subsequently diagnosed with typical MIRM after clinical and laboratory evaluations. We want to bring attention to MIRM, a recently established term in the field of differential diagnosis for drug allergies.

Accurate drug allergy diagnosis is crucial to prevent severe or potentially life-threatening reactions and to avoid unnecessary drug restrictions that can impact patients' health and lead to

increased medical expenses (4). Skin rashes are commonly seen in children treated with beta-lactam antibiotics. Many children are mistakenly labeled as penicillin-allergic, yet less than 10% of these patients develop a rash during an oral provocation test. The rash is more likely to be related to the underlying infection rather than an allergic reaction to the antibiotic (5-7). We did not think of drug allergy in our patient without the need for provocation, only on the basis of history and the nature of the rash. In the presented case early type drug allergy was not suspected as the rash that appeared one hour after the initial dose amoxicillin-clavulanic acid did not exhibit urticarial characteristics. Additionally, the rapid onset of mucosal involvement and rash also ruled out the possibility of a delayed-type reaction linked to the drug. The duration of drug induced- SJS/TEN may vary depending on the specific drug but there is typically a latent period between administration of the drug and the onset of rash (8).

Initially, the patient was admitted with a diagnosis of SJS. Although the mucosal involvement suggested SJS, the limited cutaneous involvement and the subsequent development of clinically and laboratory-confirmed pneumonia led to the suspicion of MIRM. Our case meets all the diagnostic criteria of MIRM (Table I). Key feature that help to distinguish MIRM from SJS include predominance mucosal involvement and relatively sparse cutaneous involvement and excellent prognosis. The oral mucosa is primarily affected (94%) followed by the ocular (82%) and genital mucosa (63%) characterized by vesiculobullous lesions and ulcerations (3). The patient had involvement in all three mucosal areas.

We added IVIG to the treatment due to the development of pneumonia and the need for oxygen under the steroid treatment initiated during our patient's hospitalization. In a systematic review, Lofgren et al. (9) reported that 77% of patients diagnosed with MIRM were treated with antibiotics, 37% with corticosteroids, and 11% with IVIG. Considering the low IVIG requirement reported in the literature, we believe that we may have acted hasty in initiating IVIG. Corticosteroids also have been used in the treatment of SJS/TEN for many years, but their use remains controversial. Proponents argue that high-dose corticosteroids administered early can help reduce inflammation, while opponents suggest they may increase the risk of sepsis. The available studies on corticosteroid use in SJS/TEN are all case series, mostly retrospective, with no randomized controlled trials (10). The treatment decision should be made under the guidance of experts.

Table I: Proposed diagnostic criteria for classic cases of MIRM

Detachment	<10% BSA
No. of mucosal sites involved*	≥2
Few vesiculobullous lesions, or scattered atypical targets	Yes
Targetoid lesions	±
Evidence of atypical pneumonia	
Clinical	Fever, cough, positive auscultatory findings
Laboratory	Increase in MP IgM antibodies, MP in oropharyngeal or bullae cultures or PCR, and/or serial cold agglutinins

BSA: *Body surface area,* ***PCR:*** *Polymerase chain reaction,* ***MP:*** *Mycoplasma pneumonia, *Rare cases have \ two mucosal sites involved (3).*

Our patient was hospitalized for a duration that could be considered as relatively long. The prolongation of the patient's hospitalization was caused by delayed adequate oral intake due to mucositis and the onset of pneumonia symptoms on the fifth day of hospitalization. In support of this, significant prolongation of hospitalization was observed in patients with MIRM compared to those with non-mycoplasma EM, and an increase in oxygen requirements was noted in patients with MIRM compared to those with CAP alone (11).

In patients with MIRM, while 81% of them achieve complete recovery, some individuals may experience ocular complications such as conjunctival synechiae, corneal ulcerations and dry eyes as well as oral and genital synechiae, post-inflammatory pigmentary changes, and, more rarely, complications such as B-cell lymphopenia, restrictive lung disease, and bronchiolitis obliterans have been reported (3,12-15). During the long-term follow-up of our patient, none of these complications developed.

In conclusion, MIRM is characterized by widespread mucosal involvement, minimal skin involvement, and it predominantly affects young males. When diagnosed early and supported by appropriate care, including the use of preferred treatment options such as antibiotics and systemic steroids, MIRM exhibits a favorable long-term prognosis. During the differantial diagnosis of a drug allergy it is important to keep in mind. On the other hand, since SJS/TEN is a more mortal diseases; such patients should be consulted with pediatric allergists for a definitive differential diagnosis with drug allergy; to prevent underdiagnosis of drug induced SJS/TEN.

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