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Contents

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Editorial

Dear TP readers,

Trends in Pediatrics (TP) has begun its publication life with the first issue in September 2020. TP is the official, scientific, open access publication organ of Aydın Pediatric Society. It is published quarterly in March, June, September and December. On behalf of the editorial board, we're happy to announce the publication of the second issue.

In the current issue, there are nine articles, including eight original articles and one letter to the editor. There are two original articles investigating the lung functions in young children by impulse oscillometry that provide an opportunity to assess the respiratory dynamics at an early age. The other interesting articles are related to (1) childhood pilomatrixoma, (2) testicular adrenal rest tumors in children with congenital adrenal hyperplasia, (3) complete blood count parameters of children with Kawasaki disease and viral infections, (4) the knowledge and attitudes of different populations about influenza and influenza vaccination, (5) vitamin-mineral levels of patients with Celiac disease and (6) characteristics of infections in pediatric intensive care unit. In the letter to the editor section the impact of the Covid-19 pandemic on African children was discussed. We would like to thank to the editorial team, the reviewers, all authors, and the team of Logos Publishing House for their efforts and support.

We are delighted to see the great interest of the readers to the first two issues of TP. We invite all researchers dealing with pediatric patients, including pediatrics, pediatric surgery, and child and adolescent psychiatry to involve in the upcoming issues. Please feel free to share your ideas with us, give feedbacks and comments through our web site www.trendsinpediatrics.com.

Sincerely yours,

Soner Sertan Kara

The Effect of Obesity on Asthma: Analysis of Pulmonary Function Using Impulse Oscillometry in School-age Children

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ABSTRACT

Objective: *Studies investigating the pulmonary function of school-age obese asthmatics are rare. The purpose of this study was to compare lung functions in school-age obese asthmatics and non-obese asthmatics.*
Methods: *Ninety-two children were assigned to groups of obese asthmatics (Group OA, n=43) and non-obese asthmatics (Group A, n=49) baseline impulse oscillometry test was performed to measure pulmonary functions.*
Results: *Baseline percent predicted value of R20 (p=0.025), R5-20 (p=0.040), and Fres (p=0.018) were significantly increased in obese asthmatics than non-obese asthmatics. AX was also higher in obese asthmatics compared to non-obese asthmatics, however, the intergroup difference was insignificant (p=0.787). Percent predicted value of R5 (p=0.007) and R10 (p=0.017) were higher in atopic than non-atopic obese asthmatics. Percent predicted value of R5 was higher in exercise-intolerant than exercise-tolerant non-obese asthmatics (p=0.045). Additionally, R10 was higher in non-obese asthmatics who were exposed to household mold when compared with those without exposure to household mold (p=0.045). The z scores of BMI or weight were not correlated with any one of the IOS parameters (p>0.05).*
Conclusion: *Main bronchial and peripheral airway resistance was higher in school-age obese asthmatics compared to non-obese asthmatics. Peripheral airway resistance was higher in atopic obese asthmatics as well as well as asthmatic children with exercise intolerance and household mould exposure.*

INTRODUCTION

Asthma and obesity are the two most common chronic diseases in children with increasing prevalence worldwide.[1,2] The parallel increase in the prevalence of pediatric obesity and asthma suggests a possible association between them both in children and adults.[3-6] Although, obesity-related asthma is thought to be a separate entity[7], the underlying mechanisms in children have not been fully explained. Several studies are supporting that the risk of developing asthma symptoms increases as the body mass index (BMI) increases[8-10] and asthma treatment responses can be affected by BMI.[10,11] Moreover, in the presence of obesity, the severity of asthma, the risk of asthma exacerbation, rates of hospitalization, and drug use increase.[8-9]

Spirometry is the most widely used method of analysis worldwide to evaluate pulmonary functions. It is quite difficult to apply this technique appropriately in young children because it requires high cooperation of the patient.[12] Obesity is often associated with respiratory symptoms, but many patients also have normal spirometry results. A recent meta-analysis and some large-scale studies evaluated the differences between BMI and spirometry parameters, emphasizing that obese asthmatics have different

pulmonary function dynamics.[13,14]

Spirometry is a very useful technique for measuring functions of the larger airways, but insufficient for reflecting airflow through smaller airways. In contrast, impulse oscillometry (IOS) can provide a rapid and reliable assessment of airway resistance and reactance.[15,16] It is a new and alternative technique for evaluating pulmonary function tests in pediatric patients because it is an effort-independent method and requires minimal patient cooperation. It also helps in measuring airway resistance, determining chest wall reactance, and discriminating between central and peripheral airway functions.[17,18]

Some studies have used IOS to measure pulmonary functions in asthma, but there are not enough studies evaluating pulmonary functions of children with obesity co-existing asthma.[19-21] Therefore, the purpose of this study was to assess the pulmonary function using IOS in school-age obese asthmatics and to compare it with that of non-obese asthmatics.

MATERIALS AND METHODS

Study population

This retrospective cohort study was conducted between January 2020 and March 2020 at the tertiary referral hospital pediatric allergy and immunology clinic. Ninety-two children aged between 4 and 10 were included in the study. Participants did not have accompanying respiratory tract infections and all were receiving regular inhaled steroid therapy for at least three months. Children were assigned to two groups for IOS comparison: obese asthmatics (Group OA, n=43) and non-obese asthmatics (Group A, n=49).

Definitions:

Asthma: Definition of asthma was based on the Global Initiative for Asthma (GINA) guideline criteria: paroxysmal cough, wheezing, breathlessness, or chest tightness with either an increase in FEV1 of at least 12% or 200 mL after salbutamol administration or significant airway hyperresponsiveness.[22]

Obesity: Obesity was determined based on gender and age-specific cut-off values of BMI recommended by the International Obesity Task Force.[23] BMI was calculated using the formula weight (kg)/height^2 (m). The z scores for BMI were calculated using the Turkish Children Growth Reference Centiles.[24] The zBMI cut-off value for obesity was 1.90 kg/m^2 for girls and 1.84 kg/m^2 for boys (corresponding to BMI >30 kg/m^2 in young adults).

Atopy: Atopy was defined as a positive test result either by allergen-specific immunoglobulin E (sIgE) or skin prick test (SPT). Specific IgE value to common aeroallergens (Phadiotop) was defined as a positive value when it was above 0.35. Skin prick test positivity was defined as the presence of cutaneous reaction against common allergen(s) including Aspergillus fumigatus, *Alternaria alterna*, dust mite (*Dermatophagoides pteronyssinus* or *Dermatophagoides farinae*), cockroach mix, and grass mix.

Exclusion criteria:

Patients with a past and present history of chronic respiratory diseases other than asthma, chronic cardiac and neuromuscular disease, low birth weight/preterm birth/neonatal mechanical ventilation, malignancy, immune deficiencies, connective tissue disease, acute respiratory disease in the previous four weeks, recent exacerbation of asthma, oral steroid use were excluded from the study.

Study design:

Patients' demographic characteristics, medical histories, clinical symptoms, physical examination findings, and laboratory parameters were recorded using a standard questionnaire investigating age, gender, personal or parental history of atopy, and environmental factors. Besides, allergen sIgE levels, SPT, and IOS measurement results were scanned from medical records.

All pulmonary function tests were performed in the respiratory laboratory of Pediatric Allergy and Immunology Department. The children were requested not to use short-acting beta-agonists for 8 hours and antihistamines or anti-leukotriene medications for 72 hours before pulmonary function testing.[25]

At least three acceptable IOS measurements were

taken by an experienced nurse, evaluating whether the IOS was appropriate and artificial for the entire duration of 30-second measurement.

Pulmonary Function Tests

Impulse oscillometry

A Jaeger MasterScreen IOS system (CareFusion, Yorba Linda, CA, USA) was used to measure the input impedance of the respiratory system. This procedure was performed in line with the American Thoracic Society/European Respiratory Society guidelines.[26] The main parameters included resistance (R5, R20), reactance (X5, X20), the frequency dependence of resistance calculated as the difference between resistance at 5 and 20 Hz (R5-R20, resistance at 5 Hz minus resistance at 20 Hz), resonant frequency (Fres), and area under the reactance curve (AX). Higher frequencies of R (~20Hz), reflecting the larger airways, were regarded as resistance in central airways. Lower frequencies of R (~5 Hz) provided information about the integrity of (smaller and larger) airways. Peripheral (smaller) airway resistance was defined as R5-R20.[26-28] Acceptable variability was 15%.[26] The coherence threshold was set to ≥0.6 at 5 Hz, and ≥0.8 at 20 Hz. The results for R5, R10, R20 were expressed as percent predicted values, and R5-20, AX, and Fres were expressed as crude values due to the lack of references. Baseline airway resistance (Rrs) and reactance (Xrs) at 5Hz and 20 Hz, Fres, and AX were evaluated.

Ethics

The study was approved by the local Research Ethics Committee (2020/213).

Statistical Analysis

SPSS version 22.0 statistical software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. For the estimates, significance was set at 5%, with a power of 80%, and 28 participants were considered sufficient for each group. Normality was assessed using the Kolmogorov- Smirnov test and descriptive statistics. Categorical variables were expressed as the number of cases and percentages. Continuous variables were expressed as mean values and standard deviations or median values and interquartile ranges (IQR-25 and 75 quartiles) depending on whether they were normally distributed. Nonparametric or parametric tests were performed accordingly. Comparisons of qualitative data were performed using the chi-square test, while comparisons of quantitative variables between non-obese and obese asthmatics were performed using either the Student t-test or the Mann- Whitney U test. Alpha value was set at <0.05 for all tests.

RESULTS

Ninety-two children were initially included and all of them completed the study [(49 boys (53.8%)].

A comparison of demographic data between the Group A (n=49) and Group OA (n=43) is presented in Table 1. No difference was observed between the two groups in terms of age, gender, height, history of personal, and parental atopy, co-morbid allergic or chronic diseases, exposure to environmental factors, and atopy [sIgE or SPT positivity] (p>0.05). The weight and BMI were higher in obese asthmatics than non-obese asthmatics (p<0.001 and p=0.047, respectively).

Baseline percent predicted R20 (p=0.025), R5-20 (p=0.040), and Fres (p=0.018) were significantly increased in obese asthmatics than non-obese asthmatics. AX was also increased in obese asthmatics than non-obese asthmatics, however, intergroup difference was insignificant (p=0.787) (Table 2). However, there were no differences between genders in terms of age, zBMI score, or IOS parameters (p>0.05) (Data not shown).

Percent predicted value of R5 (p=0.007) and R10 (p=0.017) were higher in atopic than non-atopic obese asthmatics. Percent predicted value of R5 was higher in exercise-intolerant than exercise-tolerant non-obese asthmatics (p=0.045). Additionally, R10 was higher in non-obese asthmatics with household mold exposure than those without (p=0.045) (Data not shown).

Correlation analysis between age and IOS parameters

The z scores of BMI or weight were not correlated with any one of the IOS parameters (p>0.05).

Age was positively correlated with percent predicted

Table 1. Comparison of demographic characteristics between the A group and OA group

Variable	A group (n=50)	OA group (n=40)	p value
Age, (years)	7 (5-9)	7 (5-10)	0.259
Gender, (% male)	24 (49%)	25 (59.5%)	0.314
Height, (z score)	0.11 (-0.51-1.07)	1.05 (0.05-1.68)	0.111
Weight, (z score)	0.16 (-0.65- 1.09)	2.37 (2.0-3.02)	<0.001
BMI, (z score)	-0.01 (-0.60-0.87)	2.04 (2.0-2.55)	0.047
Personal atopy history, (n, %)	18 (36.7%)	11 (26.2%)	0.282
Parental atopy history, (n, %)	24 (50%)	13 (37.1%)	0.245
Comorbidities			
Atopic diseases	30 (61.2%)	18 (43.9%)	0.101
Other chronic diseases	3 (6.1%)	5 (11.9%)	0.463
Exposure to environmental factors, (n, %)			
Passive smoking	20 (41.7%)	17 (47.2%)	0.612
Household smoke	17 (35.4%)	12 (33.3%)	0.842
Pet	4 (8.5%)	7 (19.4%)	0.196
Household mould	7 (14.6%)	8 (22.2%)	0.366
Allergy test positivity, (n, %)			0.282
Allergen specific IgE	10 (20.4%)	10 (23.8%)	0.339
Skin prick test	15 (30.6%)	9 (21.4%)	0.329

Abbreviations: *A group: asthma group, BMI: body mass index, IQR: interquartile range, OA group: obese asthma group, n: number, %: percentage*

Table 2. Comparison of impulse oscillometry parameters between the A group and OA group

	A group (n=50)	OA group (n=40)	p value
R5, (%)	104.79±21.95	104.16±17.98	0.883
R10, (%)	104 (92-115)	103.5 (92.5-114.25)	0.796
R20, (%)	107.26±17.62	110.04±20.31	**0.025**
R5-20, (kPa/L)	28.34±18.39	36.85±20.64	**0.040**
X5, (%)	82.85±35.10	79.83±36.19	0.687
X10, (%)	133.18±76.92	125.26±107.0	0.683
X20, (%)	-101.85±153.75	-71.24±199.88	0.412
Fres (Hz)	-135.10±33.94	119.45±27.11	**0.018**
AX (kPa/L)	1.56 (0.72-3.20)	1.90 (0.76-2.50)	0.787

Abbreviations: *A Group: asthma group, Hz: Hertz, kPa: kilopascal, L: liter, OA Group: obese asthma group, n=number, %: percent predictive value*

value of R20 (r=0.383, p=0.007) and X20 (r=0.418, p=0.003) but negatively correlated with R5-20 (r= -0.320, p=0.025) and Fres (r= - 0.420, p=0.003) in non-obese asthmatics. Similarly, age was positively correlated with percent predicted value of R20 (r=0.559, p<0.001) and X20 (r=0.451, p=0.003) but negatively correlated with R5-20 (r= -0.471, p=0.002) and Fres (r= - 0.566, p<0.001) in obese-asthmatics.

DISCUSSION

There are a few number of studies investigating the respiratory functions of school-age obese asthmatics in the literature. In this study, we assessed baseline airway resistance with reactance in school-age obese asthmatics and compared the data obtained with those for non-obese asthmatics.

The main finding of the present study was that school-age obese asthmatics exhibited higher airway resistance than non-obese asthmatics. An increase in airway resistance was determined in both central and peripheral airways. Thus, we speculated that persistent peripheral airway may be a result of low functional residual capacity and alveolar collapse due to the mass effect of fat in obesity.

Although obesity is known to affect pulmonary function, study results remain controversial for children.[29,30] Previous studies reported that BMI disproportionately impacts lung volumes and airflow among children.[31,32] Mass load of obesity can increase abdominal pressure and decrease the recoil capacity of the chest wall and may contribute to distal airway closure and reduction in lung volume.[33] The increased work of breathing and lower functional residual lung capacity may also be other possible causes.[34] Besides the mechanical effects, fat mass may negatively affect respiratory dynamics by mediating a low-grade chronic inflammation and obesity-related inflammatory mediators might exacerbate chronic airway inflammation.[35] Other possible environmental factors are sedentary lifestyle, high-calorie diet intake and low antioxidant consumption.[36] Some studies have reported that obese patients have higher airway resistance but no airway obstruction which is compatible with our results.[37] However, more research is needed, particularly considering the mechanisms underlying the relationship between asthma and obesity.

In literature, few studies have investigated pulmonary functions using IOS in children with obesity or obesity and asthma, and the findings are inconclusive. In one prospective cross-sectional study, Assumpçao et al. investigated IOS parameters among 81 children aged six to 14 years, 21 overweight, 30 obese, and 30 healthy controls. Percentage predicted values of impedance (Z5), resistance (R5), Fres, and AX representing airway obstruction were significantly higher in obese children than in the healthy controls.[38] Kalhoff et al. evaluated pulmonary functions of 518 pre-school children using IOS. R5 and X5 were mildly elevated in obese children compared to IOS reference values, but IOS values were not associated with BMI.[39] Ekström et al. reported that persistent overweight and obesity were associated with small airway obstruction with higher R5–20 and AX.[40] In another prospective study, pulmonary functions of 99 children hospitalized for bronchiolitis before the age of six months were evaluated using IOS at six years of age. Any significant differences were not observed in responses to exercise or to bronchodilators between currently obese or overweight children and normal-weight children. However, seven obese children had higher post-BD impedance in the airways and higher R5 values compared to normal-weight children.[19]

In the present study, entire airway resistance (increased R5 and R10) was found to be higher in obese asthmatics with atopic sensitivity than that without atopic sensitivity. Similarly, high airway resistance was found in those with mold allergen sensitivity (increased R10) and those with exercise intolerance (increased R5). We speculate that atopy may modify pulmonary functions by increasing airway inflammation that results in airway hyperresponsiveness and remodeling. In this regard, it comes to mind that some obesity-related mechanisms might potentiate deterioration of pulmonary function. Supporting our findings, in previous studies, higher FeNO levels reflecting higher eosinophilic airway inflammation were measured in subjects with obesity.[41]

Besides, low-level chronic inflammation caused by obesity is associated with increased leptin levels.[42] Leptin acts with Th1 cell differentiation, TNF-a, IFN-gamma, and IL-6 increase.[43] Therefore, chronic low-grade inflammation related to obesity may potentiate the effect of atopy on the deterioration of pulmonary functions in obese asthmatics more severely than that of non-obese asthmatics.

Although airway resistance was found to be higher in

obese asthmatics, there was no correlation between BMI and IOS parameters. Some studies presence of any relationship between pulmonary functions and BMI.[30,44] No effect of BMI on airway hyprereactivity was reported in a study conducted in more than 1000 children with mild to moderate asthma who were followed up to adulthood in the USA and Canada in Childhood Asthma Management Program (CAMP study).[45] Similarly, a prospective birth cohort study of more than 1000 children from New Zealand found no effect of BMI on AHR.[46] However, these studies were carried out using spirometry and there is no large-scale population study using the IOS method. Therefore, new studies are needed on this subject.

The particular strengths of the present study were that pulmonary functions and airway inflammation were examined using noninvasive methods under observation by the same highly experienced nurse and physician in all cases. All patients were examined by pediatric allergy and endocrine specialists. Treatment-naive children were included in the study to prevent potential drug interaction. Pulmonary function tests were performed at the same time of the day to eliminate the effects of potential diurnal variation.

There were also some limitations to this study. BMI is not the gold standard in assessing body composition, which is more indicative of body size than fat mass and does not distinguish fat mass from lean mass. The findings of this study should be interpreted with caution since they cannot be used to infer causality between obesity and asthma due to its cross-sectional design.

In conclusion, our findings have important implications for the interpretation of respiratory functions in school-age obese asthmatics. Obese asthmatics had higher airway resistance and measurements of pulmonary function using IOS appear to be more useful for an early understanding of the impact of obesity on lung functions of children with asthma. Our findings now need to be replicated in longitudinal studies of childhood obesity and asthma to shed further light on the complex interactions between the two entities.

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Childhood Pilomatrixoma: Case Series From a Single Center

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ABSTRACT

Objective: *Pilomatrixoma is a benign skin tumor. The aim of this study is to describe the clinical presentation and associated conditions in children with pilomatrixoma.*
Methods: *The medical records of 52 children from a single referral center obtained between 2000 and 2016 were retrospectively reviewed.*
Results: *There were a total of 62 tumors in 52 children. The mean age at excision was 9.55±4.65 years. Tumors were predominantly located in head and neck region (48.4%). There was no family history of pilomatrixoma, except one case. One patient had Turner Syndrome and the other one had tuberous sclerosis complex. Fifty-four (87%) lesions were examined by ultrasonography (USG). Pilomatrixoma was considered in the differential diagnosis in eight patients (15.3%) by a radiologist.*
Conclusion: *Pilomatrixoma is one of childhood benign skin tumors which could be detected by superficial USG method in children. It should be kept in mind for differential diagnosis in children with superficial masses.*

INTRODUCTION

Pilomatrixoma is a benign skin tumor which was first described by Malherbe and Chenantais in 1880. It was called "calcifying epitheliomas of Malherbe" because it was thought to have originated from sebaceous glands at that time.[1] In 1961, Forbis and Helwig found that the outher root sheath cell of hairy follicle was actually its source of origin. Since 1977, the terms of "pilomatrixoma" or "pilomatricoma" have been globally accepted to name the lesion.[2]

Pilomatrixoma is a benign tumor typically presents in childhood, particularly within the first decade of life.[3] The adult-onset type of pilomatrixoma has been also defined but it is often associated with nonspecific malignancies.[4] Thus, a bimodal pattern of occurrence has been reported with the first peak seen at 5-15 years and the second peak seen at 50-65 years.[5] The head and neck are the most common body regions for a pilomatrixoma. Cases outside of the head and neck region are commonly associated with genetic syndromes and disorders.[6-8] The only curative treatment of pilomatrixoma is complete excision.

The aim of this study is to (i) present our institutional experience with pilomatrixoma, describing its clinical presentation, associated conditions, radiologic and pathologic findings, and (ii) attract attention to this tumor for differential diagnosis of benign skin masses in children.

MATERIAL and METHODS

The medical records of 52 children with histologically diagnosed pilomatrixoma at plastic and reconstructive surgery department of our institution between 2000 and 2016 were evaluated retrospectively. The electronic medical records of the patients consisted of the patients' clinical medical history and pathological specimen results. Ethical approval for this study was obtained from Mersin University Faculty of Medicine (IRB No. 2000-89-102). The demographics included the patients' sex, age at operation, location of the mass, number of mass lesions (solitary or multiple), radiological findings, complications, and recurrence of the lesions. Radiological imaging results were also reviewed to analyze the characteristics of pilomatrixoma and determine their diagnostic accuracy.

Statistical Analysis

Statistical analyses were performed using the SPSS software version 24 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.). Kolmogorov-Smirnov test was used to determine the normal distribution of numerical variable. Categorical data were presented with numbers (n) and percentages (%), and numerical data with mean±standard deviation (SD) and minimum-maximum (min-max). The Pearson correlation test was used for investigating a correlation between numerical data. Type I error was determined as 5% and a p value of <0.05 was considered statistically significant.

RESULTS

Medical charts of 52 pediatric pilomatrixoma patients [24 (46.2%) male and 28 (53.8%) female] were reviewed retrospectively. The mean age at excision was 9.55±4.65 years (1-17 years). The mean tumor diameter was 2.17±1.24 cm (0.5-5.5). One of the patients (1.9%) had a family history of pilomatrixoma. One patient (1.9%) had Turner syndrome and one (1.9%) had tuberous sclerosis complex.

Multifocal disease was detected in 4 children (7.7%). The median number of synchronous lesions was 4 (3-7). Two patients (3.8%) had metachronous pilomatrixomas. The localization of 62 lesions were as follows; head and neck (n=30, 48.4%), upper limbs (n=15, 24.2%), trunk (n=11, 17.7%) and lower limbs (n=6, 9.7%). Cervical (n=14, 22.6%), preauricular (n=6, 9.7%), scalp (n=4, 6.5%) lesions, and one lesion (n=1, 3.3%) on the chin, parotid region, upper eyelid, lower eyelid, nose and cheek were surgically excised. One (1.6%) lesion was located on the areola of the breast.

The most common clinical presentation was asymptomatic, slowly growing, subcutaneous mass attached to the skin (n=56, 90.3%). The mass was mostly hard in tenderness but it was freely mobile when stretched (n=56, 90.3%). However, two children (3.8%) had discomfort and one (1.9%) had rapidly growing mass. Three patients (5.8%) had complication of acute infection. The median duration of the lesions was 6 months (6 weeks-3 years).

Fifty-four (87%) lesions were examined by ultrasonography (USG). All tumors (100%) were located in the subcutaneous layer. The median diameter of tumor was 12.8 mm (5.6-59) measured by USG. Forty-two (77.8%) lesions had oval and 12 (22.2%) lesions had irregular shape. Fourty-six (85.2%) lesions were hypoechoic and eight (14.8%) lesions were hyperechoic. Most of the lesions were also heterogeneous. All lesions had posterior shadowing. Peripheral hypoechoic rim was observed in 48 (88.9%) lesions. Echogenicity, echo texture, margin, and hypoechoic rim could not be evaluated in six (9.7%) cases of pilomatrixoma. Doppler flow signals were observed in the peripheral region in 38 (70.3%) lesions and in two (3.2%) lesions in the central region. There was no correlation between mass size and the region where Doppler flow signals were obtained ($p>0.05$). Pilomatrixoma was considered in the differential diagnosis of eight patients (15.4%) by radiologist.

The diagnosis of pathological specimens were confirmed as pilomatrixoma by pediatric pathologist in all cases except one which was diagnosed as

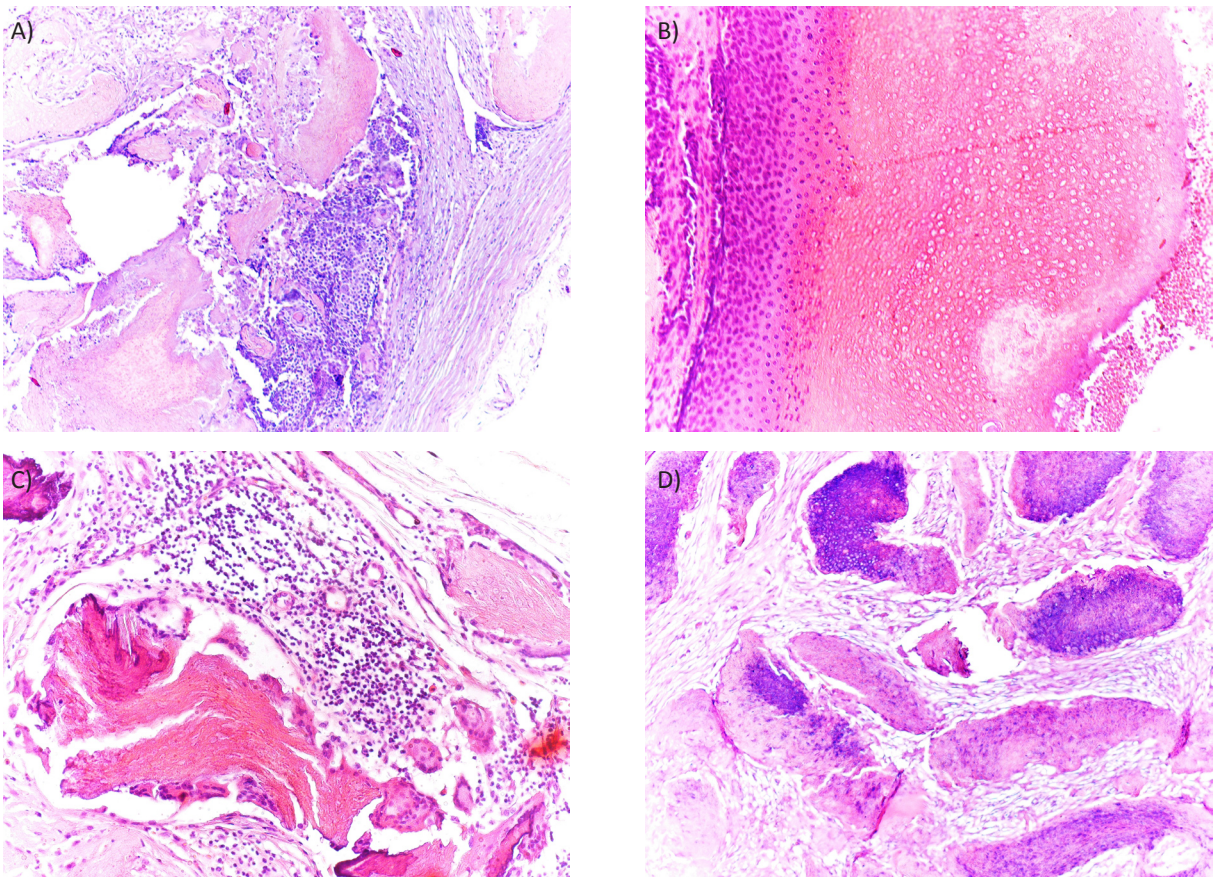

Figure 1. Typical histopathological features of pilomatrixoma (A), the tumor is composed of a biphasic population of basoloid and ghost (shadow) cells (B), maturation of basaloid cells (bottom) into ghost cells (top) the cells become larger, acquire eosinophilic cytoplasm and eventually lose their nuclei (C), epidermal cyst like structures may be present undergoing keratinization with central keratin debris. Foreign body giant cell is inflammatory reaction to keratin debris (D). The lesion may possess areas of dystrophic fine granular to larger aggregates of basophylic calcifications. [Hematoxylin-eosin, orginal magnification x100 for (A) and (D), original magnification x 200 for (B) and (C)].

dermoid cyst (Figure 1A and 1B). Epidermal cyst like structures undergoing keratinization with central keratin debris and foreign body giant cell inflammatory reaction to keratin debris were present in some cases (Figure 1C) and the calcification was seen in most cases (Figure 1D).

Recurrence of the disease was observed in two (3.8%) subjects and no recurrence was detected during the 4-year follow-up after resection.

DISCUSSION

In this observational study, the majority of tumors occurred before 10 years of age. The prevalence of pilomatrixoma is common in females, with a female-to-male ratio of 1.5-2.06.

Pilomatrixoma is typically present as a superficial, slowly and growing painless mass. It is firm but freely mobile in texture, mostly lobulated in nature, and fixed to the epidermis. The overlying skin is usually normal in appearance.[7,8] Similar to our findings, they occur mostly in the head and neck region, but rarely they can be found at any hair-bearing site, upper extremities, trunk, and lower extremities. In parallel with the literature, we observed female-male ratio around 1.2 to 1.0.

Multiple pilomatrixomas are rarely seen, but they are mostly associated with genetic disorders including familial adenomatous polyposis, myotonic muscular dystrophy, Rubinstein-Taybi syndrome, Turner syndrome, Kabuki syndrome, and childhood cancer syndrome constitutional mismatch repair deficiency.[9-15]

Neurofibromatosis type 1 was also diagnosed in patients with sporadic pilomatrixoma.[16] To the best of our knowledge, tuberous sclerosis complex was not reported to date. In this context, we reported the first case with tuberous sclerosis complex accompanying pilomatrixoma. According to Schwarz et al. the incidence of multiple lesions was 8.2-33.3%, and the lesions may be synchronous or metachronous.[17] The incidence of multiple pilomatrixoma was 7.69% and only one patient had a family history without any underlying disease in this series.

Bulman et al. reported the diagnostic accuracy of pilomatrixoma by USG as 13.3%.[18] In present study, only eight patients (15.3%) were correctly diagnosed by USG. We suggest that USG may provide limited benefits in the differential diagnosis of such lesions. It is reported that hypoechoic lesions are the most common features, as in our study.[18] In previous studies, the prevalence of hypoechoic rim that represents the capsule of the pilomatrixoma[18], was found between 65% and 75%[19-21] of the cases whereas in our study it was determined as 88.8%. In this study, Doppler USG examination could be performed in 64.5% of the lesions and vascularity was observed in 70.3% of these lesions. This is similar to the reported vascularity of 50-70% in pilomatrixomas in pediatric population.[19,21]

Pathological diagnosis of pilomatrixoma could be done with fine-needle aspiration biopsy (FNAB) or with total surgical excision. Although histological findings of pilomatrixomas are well-known, FNAB is accepted as an important method for preoperative diagnostic research. However, the cytologic diagnosis of pilomatrixoma is sometimes difficult and they are misdiagnosed.[22] For this reason, we preferred biopsy to make the diagnosis more accurately. Pathologically, there are two basic cell types, basophilic cells and eosinophilic shadow cells with an intervening connective tissue stroma containing blood vessels, foreign-body giant cells, mixed inflammatory cell infiltration and sometimes hemosiderin and rarely amyloid. We observed eosinophilic shadow cells toward the central areas of the cell masses predominantly. Calcification occurs in more than two-thirds of the tumors and is usually in the shadow cells. Calcification of the stroma occurs in about 13%; hemosiderin is found in about 25% of cases; and melanin is present in nearly 20% of lesions and may be in the shadow cells as well as in the stroma.[23] No calcification of the stroma was observed in our population.

Although pilomatrixoma is one of the most common cutaneous tumors in children and adolescent, it is usually not considered in the differential diagnosis of pediatric head and neck masses. The rate of preoperative diagnostic accuracy of pilomatrixomas ranges from 0 to 49 percent.[8] Similarly, in our most of the patients, the pilomatrixoma was not considered in differential diagnosis, only eight patients (15.3%) had correct preoperative diagnosis by USG.

In conclusion, we suggest that pilomatrixoma should be considered in the differential diagnosis of superficial or subcutaneous masses which particularly located at head and neck, particularly in children. Surgical excision of the pilomatrixoma is recommended for definitive diagnosis and curative treatment.

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Comparison of Complete Blood Count Parameters in Children with Kawasaki Disease and Viral Febrile Infections

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ABSTRACT

Objective: *Kawasaki disease (KD) is a childhood vasculitis. The inflammation of coronary arteries is the most severe complication of KD. Despite the fever, diagnosis may be delayed when clinical symptoms do not fulfill the criteria. In this study, we aimed to determine whether the complete blood count (CBC) parameters can differentiate KD from other diseases that caused fever in children.*

Methods: *The present study included 51 patients, 21 of whom were diagnosed as KD and 30 febrile non-KD patients who had viral infections. We analyzed groups' initial CBC parameters in the first visit.*

Results: *Fourteen of the 21 patients (66%) were atypical KD. There were no statistically significant differences in patients' characteristics, clinical symptoms, and signs between the groups. Six of the patients had abnormal coronary arteries like dilatation. A higher neutrophil-to-lymphocyte ratio (NLR) (2.5 (1.8-5.9) vs. 1.41 (0.89-3.6); p=0.028) and higher CRP levels (58.1 (25.6-129.3) vs. 22.8 (4.3-41.6); p=0.021) were found in KD group when compared with non- KD group. When combining NLR >1.41 and CRP >31 mg/L, there was a higher odds ratio of 24.84 (95% confident interval (2.41-198.53) of KD predicting the possibility.*

Conclusion: *Neutrophil-to-lymphocyte ratio and CRP can show inflammation and immune reactivity and they can be used to distinguish KD patients from virally infected children.*

INTRODUCTION

Kawasaki disease (KD) is a common childhood vasculitis with a high fever lasting at least five days, unresponsive to antibiotic and antipyretic treatments used. The inflammation of coronary arteries is the most severe complication of KD.[1] Although systemic inflammation has a significant role in KD pathogenesis, there is no specific disease marker. Kawasaki disease is still diagnosed based on clinical features. Clinical features are bilateral conjunctivitis, unilateral cervical lymphadenopathy, erythema and edema on the feet and hands, strawberry tongue, and lip fissures. Only prolonged fever (≥5 days) together with two or three clinical criteria may be used to diagnose incomplete KD.[2]

Leukocytes are essential mediators in the inflammation process, and changes in their numbers reflect the immune system's response to systemic inflammation.[3] Neutrophils are mostly considered a marker of ongoing general inflammation, while

lymphocytes are considered a regulator of the immune system.[4] Although neutrophils are dominant in the acute fever period, leukocyte counts increase in patients with KD.[1,5,6] Fever is frequent during bacteremia and viral infections as pro-inflammatory cytokines such as tumor necrosis factor (TNF-α), interleukin 1 (IL-1), and IL-6 induce fever.[7] Parameters such as the NLR already rise during the febrile period due to these cytokines. In a review, peripheral blood leucocyte ratios are shown to be helpful biomarkers that reflect viral and bacteremia infections.[8]

Unfortunately, the value of complete blood count (CBC) parameters for predicting KD has never been compared with non-KD children with fever due to bacteremia and viral infections. The present retrospective study was performed to determine whether the CBC parameters can differentiate KD from infected children with fever.

MATERIAL and METHODS

The medical data of KD patients at the hospital were reviewed from January 2017 to September 2020. The study was approved by the Ethics Committee of Adnan Menderes University (Turkey) (2020/229). Five principal clinical manifestations and including fever >38°C were used to diagnosed KD. When clinical manifestations did not fulfil criteria, and other diseases could be excluded, incomplete KD was diagnosed.[2] Neutrophils and leukocyte counts were measured during the acute febrile phase using the same automated blood cell counter. Intravenous immunoglobulin (2 g/kg) was used to treat all KD and incomplete KD patients. Acetylsalicylic acid (ASA) treatment was started at a dose of 80-100 mg/kg/day along with IVIG. The ASA dose was reduced to the antiaggregant dose (3-5 mg/kg/day) during the convalescent period. Acetylsalicylic acid treatment was continued for an average of 21 days or less according to the clinical condition of the patient. We repeated IVIG treatment if the fever continued despite the first IVIG therapy. Intravenous immunoglobulin resistance was defined as fever continued (>24h) after IVIG.

In this study, we compared CBC parameters of patients with KD and virally infected children who had fever longer than four days and did not meet AHA diagnostic criteria. The non-KD group consisted of children with viral upper respiratory tract diseases. We also excluded non-KD patients with suspected infectious diseases, including Epstein-Barr virüs infection, adenovirus infection, bacterial cervical lymphadenitis, or scarlet fever.

SPSS version 20 (SPSS, Inc., Chicago, Illinois) was used to analyze. Data are expressed as mean±SE or as percentages, as appropriate. The chi-square tests for nominal data, unpaired Student's t-tests for continuous data, and paired Student's t-tests for leukocyte profiles were used to perfom. To assess NLR's predictive value in KD, curves and the most discriminating cut-off values were identified. The multivariate logistic regression analysis was used to test significant differences between the groups on univariate analysis. A p-value under 0.05 was considered statistical significance.

RESULTS

The present study included 51 patients, including 21 KD and 30 controls, who were non-KD patients with fever due to infections. Fourteen of the 21 patients (66%) were atypical KD on the diagnosis. Six (42%) of atypical KD patients and 2 (28%) KD patients had abnormal coronary arteries like dilatation. IVIG treatment was repeated because fever continued in three patients despite first IVIG therapy. After the second IVIG therapy, the fever of these patients also decreased. We could not compare IVIG-responsive and IVIG-resistant groups due to the small numbers of IVIG-resistant group.

The mean ages were 2.8 (1.9-4.6) and 1.9 (1.4-4.2) years, and the duration of fever was 4.2 (3-6) and 4.4 (3-6) days for KD and non-KD groups, respectively. There were no statistically significant differences between patients' characteristics (Table 1). There were a higher NLR (2.5 (1.8-5.9) vs. 1.41 (0.89-3.6); p=0.028) and higher CRP levels (58.1 (25.6-129.3) vs. 22.8 (4.3-41.6); p=0.021) (Table 2).

ROC curve presented NLR>1.41 (sensitivity 92%, specificity 49.4%, p=0.017, Odds ratio 1.56, 95% confident interval (1.22-1.84) and CRP>31 mg/L

Table 1. Patients' characteristics and clinical symptoms

Groups	KD (n=21)	Non-KD (n=30)	p
Age [year; median (IQR)]	2.8 (1.9-4.6)	1.9 (1.4-4.2)	0.16
Gender	12M/9F	16M/14F	0.48
Days of fever* [median (IQR)]	4.2 (3-6)	4.4 (3-6)	0.24
Oral change	15 (75%)		
Skin rash 0.143	11 (55%)		
Lymphadenopathy	4 (20%)		
Extremity change	5 (25%)		
Non-exudative conjunctivitis	12 (60%)		

*Some datas are presented by percentage and median with interquartile range (IQR). *p<0.05*

Table 2. Patients' laboratory data

Groups	KD (n=21)	Non-KD (n=30)	p
WBC (x1000/mm^3)	12 (7.8-14.2)	12.5 (8.4-15.4)	0.594
Hemoglobulin (g/dL)	12.4 (11.7-12.8)	12.5 (11.6-13.1)	0.4810
Lymphocyte (%)	30.6 (18.3-29.6)	39.9 (28.2-51.4.)	0.043*
Neutrophil (%)	66.5 (53.6-81)	51.1 (33-61.5)	0.041*
Neutrophil to lymphocyte ratio	2.5 (1.8-5.9)	1.41 (0.89-3.6)	0.028*
Platelet (x1000/mm^3)	325.4 (158.2-402.4)	316.4 (282.5-401.6)	0.75
CRP (mg/L)	58.1(25.6-129.3)	22.8 (4.3-41.6)	0.021*

*The data are presented by percentage and median with interquartile range (IQR). *p<0.05*

Table 3. The multivariate and univariate analyzes of KD group

	Sensitivity	Specificity	p-value	Odds ratio (95% confident interval)
NLR>1.41	92%	49.4%	0.017*	1.56 (1.22-1.84)
CRP>31 mg/L	83%	61%	0.021*	11.6 (1.21-118.5)
NLR>1.41 and CRP>31 mg/L	84%	73.4%	0.001*	24.84 (2.41-198.53)

*NLR: Neutrophil to lymphocyte ratio. *p<0.05*

(sensitivity 83%, specificity 61%, p=0.021. Odds ratio 11.6, 95% confident interval (1.21-118.5)), When combining NLR> 1.41 and CRP> 31 mg/L, there was a higher odds ratio of 24.84 (95% confident interval 2.41-198.53) of KD prediction possibility (Table 3).

DISCUSSION

An accurate diagnosis of KD is essential because of the possibility of life-threatening complications. Despite of well-established diagnostic criteria, KD diagnoses are still challenging, especially for incomplete KD forms.[9]

Neutrophils show increased inflammatory mediator secretion while lymphocytes represent immune regulatory response.[4] NLR and PLR are helpful predictors in IVIG resistance patients with KD.[10-12] Yan and et al.[13] compared with KD and suspected KD patients, and similar to our results, they claimed that the cut-off value of NLR of 1.33 has a high sensitivity predictive value for KD.

In the present study, the cut-off value of NLR of 1.41 has an odds ratio of 1.56 (1.22-1.84) has a predictive value to KD's diagnosis. This value has a higher sensitivity to diagnose KD.

According to AHA guidelines for incomplete KD diagnosis, ESR ≥40 mm/hour and/or CRP >30 mg/L

are thought supplementary laboratory data.[14] In this study, we used CRP levels to show inflammation status and they they can also be a discriminative factor. We showed that the CRP>31 mg/L could be used as a predictive value with an odds ratio of 11.6 (95% confident interval 1.21-118.5, sensitivity 83%, specificity 61%, p=0.021).

During inflammatory conditions as in infectious diseases CRP levels are elevated. Clinicians must be careful to evaluate CRP levels and rule out other systemic inflammation diseases and infections because CRP level >31 mg/L is commonly seen during inflammatory diseases and infections in children. So, we combined the cut-off values of NLR and CRP to determine a higher odds ratio. When combining NLR >1.41 and CRP >31 mg/L, there was a higher odds ratio of 24.84 (95% confident interval (2.41-198.53) of KD predicting possibility. It has a lower sensitivity but better specificity than using NLR or CRP alone. As presented in the present study, the febrile days ranged from 3 to 6 days. Therefore, if patients had a fever longer than three days, NLR and CRP should be evaluated as early as when suspected from KD.

This study has some limitations. First, this study was a retrospective study. Second, although the causes of fever in the controls were attributed to viral infections, the definitive diagnosis with molecular/serolojical tests could not be made. Further studies should focus on the CBC parameters that can discriminate KD from children with other infections and healthy children.

CONCLUSION

When clinicians suspect KD, we recommend checking CRP and NLR values if the patients had a fever longer than three days. Their odds ratios can ensure clinicians with a beneficial tool for discrimination. The neutrophil-to-lymphocyte ratio is a cheap and simple test. The neutrophil-to-lymphocyte ratio and CRP can be used to distinguish KD patients from virally infected children.

Ethics Committee Approval: The study was approved by the Ethics Committee of Adnan Menderes University (3.12.2020/229).

Conflict of Interest: The study was approved by the Ethics Committee of Adnan Menderes University (Turkey).

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Impaired Lung Functions Using Tidal Breath Analysis in High-risk Infants with Recurrent Wheezing

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ABSTRACT

Objective: *We aimed to investigate lung functions using tidal breath analysis (TBA) in high-risk infants with recurrent wheezing.*
Methods: *Lung functions measured using TBA in infants with physician-diagnosed recurrent wheezing (≥3 episodes) who applied our institution between 2018-2020, were retrospectively analyzed. Infants were assigned to two groups: high-risk infants with recurrent wheezing (n=30) and wheezy infants without high risk of atopy (n=33).*
Results: *High-risk infants with recurrent wheezing had lower mean values of tPTEF, tPTEF: tE, VPTEF, and VPTEF: VE than that of wheezy infants without high risk of atopy. There was no significant difference between two groups in terms of Vt/kg and respiratory rate. ROC curve analysis showed that tPTEF: tE ratio <26.5 demonstrated 63.3% sensitivity and 63.6% specificity for detection of high risk of atopy.*
Conclusion: *This study showed that high-risk infants with recurrent wheezing have lower lung function than those of wheezy infants without high risk of atopy. TBA might be useful method to evaluate lung function in wheezy infants.*

INTRODUCTION

Wheezing is common in children and more than 30% of children suffer from wheezing before their third birthday.[1] It is not clear how this problem which is seen in early period, will progress to the advanced age of the child. Many wheezing infants have only a transient type of disease, however, approximately 40% of them will demonstrate asthma during school age.[2] Objective tools which could predict prognosis in these infants will assist in making the therapeutic decisions.[3] Tidal breath analysis (TBA) in wheezy infants, has been shown to predict subsequent wheezing illnesses.[4,5]

TBA is a new technique that has been used in a limited number of research centers, especially in measuring respiratory functions in infants. TBA is a repeatable method that allows the measurement of airway obstruction and tidal capacity during effortless spontaneous breathing in infants. This method is (i) noninvasive, (ii) does not require cooperation and (iii) does not require sedation.

The presence of family history of atopy has been accepted as a risk factor for the onset of respiratory symptoms in infants.[6] Although several risk factors for developing asthma in wheezing infants have been identified, the relevance of assessing lung function in these high risk infants remains unclear. Studies are needed to determine the effect of family history on lung function in infants. Accordingly, in

this study we aimed to investigate TBA in wheezy infants with high risk for atopy and to compare their data with wheezy infants without high risk of atopy.

MATERIAL and METHODS

Subjects

This retrospective study was conducted between January 2018 and March 2020 at the outpatient clinic of pediatric allergy and immunology at the Aydın Adnan Menderes University. The study was approved by the Institutional Ethics Committee (No: 2020/228). Infants with recurrent wheezing (≥3 episodes of physician verified wheeze) were assigned to two groups: (i) wheezy infant with positive family history of atopy (high risk group): with at least one parent or sibling with physician-diagnosed asthma, allergic rhinoconjunctivitis, atopic dermatitis, allergic urticaria and food allergy, and (ii) wheezy infant without positive family history of atopy.

The exclusion criteria were as follows: Prematurity (<370/7 weeks), small for gestational age, known history of bronchopulmonary dysplasia, major congenital anomalies, neuromuscular diseases, infants delivered to mothers who gave a history of smoking, congenital heart diseases, any chronic lung disease, any previous non-respiratory infection, immunodeficiency, exposure of passive smoking, chronic disease, respiratory infection within 3 weeks, infants who received corticosteroid or bronchodilator treatment before three weeks.[7]

Tidal breath analysis measurements

Tidal breath flow obtained with a commercially available portable pediatric lung function device (MasterScreen PAED, CareFusion, Germany). The flow was measured by a non-heated pneumotachograph with a flow range of 0-10 L/min (Hans Rudolph Inc, USA). The system was checked for leakage after the transparent facemask (Rendell-Baker, Soucek) was placed on the face.[8,9] A thin sealing ring of silicon putty was effective in prevention of air leaks. Dead space for the pneumotachograph and system was 1.66 mL and 2.4 mL, respectively. Standard calibration of the system was performed by the experienced practitioner with a 100 mL calibration syringe before each recording session. All the measurements were performed in the early morning time (between 09:00-12:00 am) after 30 minutes of feeding during natural and quiet sleep. Any sedative drugs such as chloral hydrate and triclofos sodium solutions were not given. The face mask was placed and recordings began after quiet sleep which defined as regular respirations, no eye movement, and no overt motions. Recording was stopped when any movement of the body, rapid eye movements, hiccups, or impaired rhythm of breathing is observed. The ambient temperature was maintained at 22-25°C. Recording was made after a sufficient adaptation period (for 2-3 minutes) had been allowed to regular respiration.[10,11] Depending on the variability of the breathing pattern, at least 60 inspiratory and expiratory breath cycles were measured as the flow-volume curve considered as an epox.[8,9] The respiratory pattern in which at least 20 regular epox cycles were evaluated. All epox values were recorded and averages were calculated separately by two different researchers. The parameters were measured with each breath of the infant and a diagram consistent with the breath was formed. The average value was measured after at least 20 consecutive artifact-free breaths and the best three values were selected.[12] Parents were always accompanied their infants during the measurement.

The main parameters of tidal breath include; time to peak tidal expiratory flow (tPTEF), peak tidal expiratory flow (PTEF), expiratory time (TE), time to reach peak tidal expiratory flow to total expiratory time (tPTEF:tE), tidal volume (VT), inspiratory time (Ti), expiratory flow when %75, 50% and 25% of tidal volume remains in the lungs (TEF75, TEF50, and TEF25), respiratory rate (RR), exhaled volume to peak tidal expiratory flow (VPTEF), the volume until peak tidal expiratory flow to total expiratory volüme (VPTEF:VE) and total expiratory volume (VE). All parameters were calculated by the tidal breath analyze device computer.

Statistical Analysis

Statistical analyses were performed using the SPSS software version 24 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.). Categorical data were presented with n and %, and numerical data with mean±standard deviation if normally distributed, and median (IQR) if non-normally distributed. Descriptive statistics

(kurtosis and skewness), visual methods (histogram), and analytical tests (Shapiro-Wilk test) were used to determine the normal distribution of numerical variables. Chi-square tests were used for comparison of categorical data. In the comparison of independent 2 groups, student t test was used if the data was normally distributed, and Mann Whitney U test was used if the data were non-normally distributed. Spearman correlation test was used for the associations between numeric data. Receiver Operating Curve (ROC) analysis was used for some breath parameters in predicting presence of high risk. When a significant cut-off value was detected the sensitivity, specificity and area under curve statistics were presented. A linear regression model was used to identify independent predictors of tPTEF:tE. Type I error was determined as 5% and a p value was<0.05 was considered statistically significant.

RESULTS

a. Patient Characteristics

A total of 63 wheezy infants aged 8–23 months were included in this study. The characteristics of the wheezy infants are summarized in Table 1. There was no significant difference between two groups in terms of age, gender, weight, and height.

Table 1. Demographic characteristics of the infants*

Gender	
Female	27 (42.9)
Male	36 (57.1)
Age (month)	16.0 (11.0-23.0)
Weight (kg)	10.6±2.8
Height (cm)	78.8±9.1
Mother Astma	
Yes	47 (74.6)
No	16 (25.4)
Non-Asthmatic Atopy in the Mother	
Yes	57 (90.5)
No	6 (9.5)
Father Astma	
Yes	57 (90.5)
No	6 (9.5)
Non-Asthmatic Atopy in the Father	
Yes	61 (96.8)
No	2 (3.2)
Sibling Astma	
Yes	58 (92.1)
No	5 (7.9)
Stove Heating at Home	
Yes	53 (84.1)
No	10 (15.9)
Household Pets	
Yes	60 (95.2)
No	3 (4.8)

Data were presented as n (%) or mean±standard deviation if normally distributed, and median (IQR) if non-normally distributed
Abbrevations: kg, kilogram; cm, centimeter; IQR, interquartile range

b. Measurement of lung function

The comparison of TBA parameters between high-risk infants with recurrent wheezing and wheezy infants without high risk of atopy are shown in Table 2. The parameters of tPTEF, tPTEF:tE, VPTEF, VPTEF:VE were significantly lower in infants with high risk when compared with the infants with no risk (p< .05). Although VT/kg was lower in infants with high risk than no risk, the difference was not significant (p= .11).

Age was positively correlated with tPTEF, tPTEF:tE and VPTEF [(r= 0.448, p< 0.001), (r= 0.310, p= 0.014) and (r= 0.709, p< 0.001) respectively] (Table 3).

Table 2. Comparison of high-risk infants with recurrent wheezing and wheezy infants without high risk of atopy*

	High Risk (n=30)	No Risk (n=33)	p†
Gender			
Female	11 (40.7)	16 (59.3)	
Male	19 (52.8)	17 (47.2)	0.344‡
Age (month)	15.5 (8.0-22.0)	17 (12.0-23.0)	0.347§
Weight (kg)	11.0±3.4	10.3±2.1	0.350
Height (cm)	77.7±10.4	79.7±7.7	0.389
tPTEF	0.2 (0.2-0.3)	0.4 (0.3-0.4)	0.002§
tPTEF:tE	24.0±9.9	31.4±12.3	0.011
VPTEF	21.55 (16.5-31.7)	31.8 (22.0-41.9)	0.030§
VPTEF:VE	27.3±7.9	32.8±10.3	0.022
MV	2.3 (2.0-3.9)	2.6 (2.2-3.4)	0.826§
VT/kg	8.8±2.1	9.6±2.1	0.110
IT/ET	0.7±0.1	0.7±0.1	0.490
RR	30.6 (24.3-42.6)	26.7 (23.4-32.4)	0.280§
TEF75	128.9±41.2	115.9±45.1	0.240
TEF50	112.6±39.5	108.9±44.0	0.731
TEF25	69.0 (54.0-98.0)	75.0 (61.0-103.0)	0.545§

**Data were presented as n (%) or mean±standard deviation if normally distributed, and median (IQR) if non-normally distributed*
†Data analysis was held by Student's t test
‡Data analysis was held by Pearson chi-square test
§Data analysis was held by Mann Whitney U test
Abbrevations: kg, kilogram; cm, centimeter; tPTEF, time to peak tidal expiratory flow; tPTEF:tE, rate of time to reach peak tidal expiratory flow; VPTEF, volume expired before PTEF was attained; VPTEF:VE, ratio of volume until peak tidal expiratory flow to total expiratory volume; MV, minute ventilation; VT, tidal volume; IT, inspiratory time; ET, expiratory time; RR, respiratory rate; TEF75, TEF50, and TEF25, expiratory flow when 75%, 50%, and 25% of tidal volume remain in the lungs; IQR, interquartile range

Table 3. Correlation between breath parameters and age*

Parameter	Age	tPTEF	tPTEF:tE	vPTEF
1. Age	–			
2. tPTEF	0.448 (<0.001)	–		
3. tPTEF:tE	0.310 (0.014)	0.667 (<0.001)	–	
4. vPTEF	0.709 (<0.001)	0.766 (<0.001)	0.686 (<0.001)	–
5. vPTEF:vE	0.243 (0.055)	0.642 (<0.001)	0.945 (<0.001)	0.699 (<0.001)

**Data were presented as Spearman's rho (p value)*
Abbrevations: *tPTEF, time to peak tidal expiratory flow; tPTEF:tE, rate of time to reach peak tidal expiratory flow; VPTEF, volume expired before PTEF was attained; VPTEF:VE, ratio of volume until peak tidal expiratory flow to total expiratory volume*

Table 4. Predictors of tPTEF:tE

Parameter	β	95% CI	t	p
Constant	10.116	-0.098 – 20.329	1.981	0.052
Age	0.477	0.086 – 0.869	2.440	0.018
Risk	6.586	1.087 – 12.086	2.396	0.020

F=6.687, p=0.002, adj. R^2:

A multiple linear regression was calculated to predict tPTEF:tE based on their age and risk. A significant regression equation was found (F(2,60)=6.687, p=0.002) with an R2 of 0.182. Participants' predicted tPTEF:tE is equal to 10.116+0.477 (age) + 6.586 (risk), where risk is coded as 1=high risk, 2=no risk, and age is measured in months. Participant's tPTEF:tE increased 0.477 for each month of age, and no risk is 6.586 more than high risk. Both age and risk were significant predictors of tPTEF:tE (Table 4).

According to the ROC curve analysis to estimate optimal cut-offs to predict being wheezy infant with high risk for atopy: (a) tPTEF ≤ 0.27 demonstrated 70.0% sensitivitiy and 69.7% specificity with an AUC:0.723 (CI:0.595-0.851, p=0.002), (b) tPTEF:tE <26.5 demonstrated 63.3% sensitivitiy and 63.6% specificity with an AUC:0.687 (CI:0.556-0.817, p=0.011), (c) VPTEF <23.0 demonstrated 60.0% sensitivitiy and 69.7% specificity with an AUC:0.659 (CI:0.523-0.795, p=0.030), and (d) VPTEF:VE <29.0 demonstrated 63.3% sensitivitiy and 63.6% specificity for detection of high risk with an AUC:0.670 (CI:0.537-0.803, p=0.020) (Table 5).

DISCUSSION

In the present study, we demonstrated a significant lung function impairment in wheezy infants with high risk for atopy than that of wheezy infants without high risk of atopy. The airflow tPTEF, tPTEF:tE) and lung volumes (VPTEF, VPTEF:VE) were lower in wheezy infants with high risk for atopy compared to those wheezy infants without high risk of atopy. However, there was no significant difference between two groups in terms of Vt/kg and respiratory rate. Additionally, ROC curve analysis showed that tPTEF:tE ratio <26.5 demonstrated 63.3% sensitivity and 63.6% specificity for detection of high risk.

The TBA parameter of tPTEF:tE is associated with the initial portion of tidal breath expiration, until the point of peak flow. A few studies have reported that

Table 5. Cut-off criterion values and coordinates of the ROC curve of high risk and no risk groups

Parameter	Cut-off	Sensitivity	Specificity	AUC	95% CI	p
tPTEF	≤0.27	70.0	69.7	0.723	0.595-0.851	0.002
tPTEF:tE	<26.5	63.3	63.6	0.687	0.556-0.817	0.011
VPTEF	<23.0	60.0	69.7	0.659	0.523-0.795	0.030
VPTEF:VE	<29.0	63.3	63.6	0.670	0.537-0.803	0.020

Abbrevations: *AUC, area under curve; CI, confidence interval; tPTEF, time to peak tidal expiratory flow; tPTEF:tE, rate of time to reach peak tidal expiratory flow; VPTEF, volume expired before PTEF was attained; VPTEF:VE, ratio of volume until peak tidal expiratory flow to total expiratory volume*

a decrease in tPTEF:tE ratio which indicates obstructive airway diseases. Dezateux et al.[13] demonstrated that the mean value of tPTEF:tE was lower in wheezy infants than healthy infants. Zedan et al.[7] demonstrated that, wheezy infants with positive parental history of asthma and high eosinophilic percentage showed a significant decrease in tPTEF:tE compared to healthy infants. Carlsen et al.[14] found that VPTEF:VE was significantly lower in asthmatic children compared to healthy infants before bronchodilator administration. Also, Morris et al.[15] demonstrated that, the ratio of tPTEF:tE and VPTEF:VE were significantly lower in children with obstructive airway disease. In the present study, in the high-risk group the mean tPTEF:tE (0.24) was the same as reported by Martinez et al.[16] in the group of (sedated) infants who subsequently developed wheezing.

We speculate that, decreased tPTEF:tE ratio in high-risk infants might be related to narrowing of the airway size. The increase of these parameters after bronchodilator inhalation in children with obstructive airway diseases supports this hypothesis.[17] Several studies have observed an increase in tPTEF:tE ratio after bronchodilators inhalation in infants[18,19], so this improvement may be a result of the bronchial hyperreactivity. Consequently, in wheezy infants with high risk, a decrease in tPTEF:tE may be a valuable finding in predicting the development of asthma.

In the present study, the wheezy infants with high risk for atopy had no clinically detectable bronchial obstructionat the physical examination with a normal range of respiratory rate. Additionally, there was no correlation between the respiratory rate and other TBA parameters.

Thus, it was demonstrated by the TBA method that wheezy infants with high risk for atopy in this study had a subclinical bronchial obstruction despite normal respiratory rate.

The strengths of our study include well defined high-risk infants that were not exposed to smoke, the collection of data using meticulous methodology by the same experienced staff under the same conditions, which adhered to international guidelines and tight quality control during the study. The major limitations of the present study were the relatively small sample size and the lack of long-term follow up of the infants. Although, maternal or paternal history of atopy was recorded, its effect on TBA could not be evaluated due to small sample size.

In this study, subclinical bronchial obstruction was accurately demonstrated by the TBA technique in wheezy infants with high risk of atopy compared to wheezy infants without a high risk of atopy. Thus, it has been shown that being at high risk for atopy in the early years of life is associated with bronchial obstruction. Therefore, we suppose that obtaining a more detailed history of atopy from the parents and/or siblings may help us to predict the risk of early asthma development in this particular population. Additionally, TBA is a non-invasive, repeatable, easy method for assesment of lung function at an early age and is a potential candidate for subsequent asthma prediction. Further studies conducted with a long follow-up period will be helpful to demonstrate the association between wheezy infants with high-risk for atopy and lung function abnormalities.

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Testicular Adrenal Rest Tumors in Patients with Congenital Adrenal Hyperplasia: A Case Series

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ABSTRACT

Objective: *Testicular adrenal rest tumors (TARTs) are the main etiology of infertility in congenital adrenal hyperplasia (CAH). The aim of this study is to determine the patients diagnosed with TART and to evaluate the risk factors associated with the development of the disease.*
Methods: *Clinical characteristics of 31 patients with CAH including 19 male, and 12 female patients who were followed up in our clinic were retrospectively reviewed regarding the presence of TART. Differences between clinical and laboratory findings of patients with and without TART were examined. Six male patients with TART were included in the study. Clinical characteristics such as pubertal stage, treatment doses, laboratory findings were evaluated. Changes in size of TARTs were examined with ultrasound follow-ups at six month- intervals.*
Results: *The prevalence of TARTs was 31.5 % (6/19 male). Precocious puberty was higher in patients with TART than without TART. The mean age of the patients was 9.1±2.4 (range: 5.2-12.4) years at the time of diagnosis with TART. Five patients with TART were inadequately controlled. Four patients had a history of precocious puberty. Tumor progression was detected in 4 of 6 patients. In three patients with tumor progression, serum 17-hydroxy progesterone (17-OHP) values increased during follow-up, probably due to non-compliance with treatment.*
Conclusion: *Scrotal ultrasound monitoring should be performed in all male patients with CAH in early childhood irrespective of disease control.*

INTRODUCTION

Congenital adrenal hyperplasia (CAH) belongs to a group of autosomal recessive disorders caused by the deficiency of one of the enzymes involved in adrenal steroidogenesis. More than 90% of the cases have 21-hydroxylase enzyme deficiency caused by CYP21A2 mutation.[1,2]

One of the most serious long- term complications of 21-hydroxylase enzyme deficiency is benign testicular tumors, called TART.[1] The etiology and pathogenesis of TARTs are not fully elucidated. Common adrenogenital primordium-derived undifferentiated adrenal cells are thought to remain in the testicular parenchyma and lead to tumor formation by chronic ACTH stimulation.[3,4]

Poor hormonal control seems to be associated with TART. Decreasing ACTH levels with high-dose glucocorticoid therapy causes shrinkage in testicular adrenal rest tumors. However, in some cases, high dose steroid therapy does not reduce tumor size. Moreover, TARTs can also be seen in well-controlled patients with CAH. These findings suggest that, factors other than hormonal control may cause tumor formation and growth.[5-7] Adrenal-specific enzymes (CYP11B1 and CYP11B2), ACTH, angiotensin 2 and LH receptors were detected in tumor tissue. Increase in pubertal LH has been reported to contribute to tumor growth through LH receptors in tumor tissue. Increase in the frequency of TART in well-controlled patients after puberty is attributed to this condition.[1]

The frequency of TARTs was reported to range between 14% and 86% in different studies.[1,8] Most cases in the literature are detected in the pubertal period and in generally poorly controlled patients.[5]

Tumors with a size of <2 cm are usually not noticed by palpation. Ultrasonography (USG) is the gold standard method of detection. Additional methods such as magnetic resonance imaging (MRI) should be used in smaller and suspicious lesions.

The aim of this study is to determine the patients diagnosed with TART by testicular ultrasound in our clinic and to evaluate the factors associated with the development of the disease such as its clinical manifestations, disease control and presence of puberty.

MATERIAL and METHODS

The study was conducted in pediatric endocrinology outpatient clinic of the university. Medical records of the patients followed with the diagnosis of CAH between January 2012 and September 2020 were retrospectively reviewed. In our clinic, anthropometric measurements, physical examination, and hormone assays of patients with CAH are performed every three months during the follow-up period.

Adequate control of CAH was defined as having a mean serum level of 17-hydroxyprogesterone (17-OHP) ≤10 ng/mL and age appropriate growth during the follow-up period.

Serum ACTH, renin and androstenedione levels were measured by chemiluminescence immunoassay (CLIA). Serum 17-OHP and aldosterone levels were measured using radioimmunoassay (RIA).

Pubertal development was evaluated according to Tanner staging. Bone age assessment was reported by a pediatric endocrinologist according to the Greulich and Pyle method.

TART investigation was performed by scrotal ultrasonography obtained in a Siemens Acuson Antares (5–13 MHz) at six- month intervals during follow-up period.

The statistical analysis was conducted with IBM SPSS Statistics 20 (IBM Corp., New York, USA). Descriptive analysis was performed and data were further analyzed using Mann-Whitney U and chi-square tests. For all tests, the level of significance was set at $p < 0.05$.

RESULTS

Nineteen male patients with CAH who were followed up in our clinic were included in the study. One patient was followed up with 11-hydroxylase deficiency, two with simple virilizing type, and 16 with classical salt-wasting type 21-hydroxylase deficiency. TART was diagnosed in 6 (31.5%) of the patients screened by ultrasound. All six patients with TART had salt -wasting type 21-hydroxylase deficiency.

The characteristics of patients with and without TART are summarized in Table 1. The prevalence of precocious puberty was higher in patients with TART than patients without. Other laboratory and clinical

Table 1. Comparison of clinical and laboratory characteristics of the patients with and without TART

	TART (+)	TART (-)	p value
Age at the time of CAH diagnosis (year)	0.15 (0.10-0.20)	0.25 (0.10-4.6)	0.105
Weight (SDS) kg	1.8 (-0.2-2.3)	0.5 (-0.2-0.9)	0.302
Height (SDS)	1.4 (-0.18-2.8)	-0.82 (-1.8-0.7)	0.119
Height velocity (SDS)*	-0.7 (-0.1- -2.1)	-0.3 (-1.08-0.17)	1.000
BMI (SDS)*kg/m^2	1.4 (0.1-1.8)	1.4 (0.4-2)	1.000
17-OHP level (ng/ml)*	5 (2.7-19.1)	4.5 (3.8-9.5)	1.000
Renin (ng/ml/h)*	38.4 (12.8-124.9)	3.7 (0.94-6.9)	0.119
Aldosterone (ng/dl)*	92 (24.2-140.2)	5.5 (2.9-25.3)	0.242
Hydrocortisone dose (mg/m^2/day)*	14.4 (10.5-16.4)	11.7 (9.3-14.2)	0.608
Fludrocortisone dose (mg/day)*	0.1 (0.08-0.11)	0.08 (0.05-0.11)	1.000

** mean of the last 1 year*

Table 2. Clinical, laboratory and ultrasonography characteristics of the patients with TART

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Median (min-max)
Genotype	I2splice	I2splice+ V281L+P453S	NA	NA	NA	I2splice/ del8bpE3	
Age at the time of CAH diagnosis (day)	10	60	30	24	15	15	19.5 (10-60)
Age at the time of TART diagnosis (decimal year)	5.2	10.1	9.1	7.9	12.4	10.1	9.66 (5.25-12.41)
BA-CA *(years)	-0.75	2.84	4.84	6.09	-	2.34	2.84 (-0.75-6.09)
Age at the time of onset of puberty (years)	-	8.9	NA	6.6	NA	6	NA
Follow-up time with usg (years)	-	4.6	2	4.3	4.3	6	4.2 (2-6)
TART size (mm)**	NA/NA	-/3	NA/NA	12/14	13/12	4/5	
Tanner stage *	1	2	2	2	4	2	
Precocious puberty	-	+	+	+	-	+	
17-OHP level (ng/ml)***	3.5	5.26	32.4	4.75	0.33	19.6	5 (0.33-32.4)
ACTH level (pg/ml) ***	139	13.1	16.2	7.69	41.16	44.8	28.9 (7.69-139)
Androstenedione level (ng/ml)***	0.46	NA	6.65	NA	NA	1.9	1.9 (0.46-6.65)

** at the time of TART diagnosis, **at the first diagnosis, long diameter, right/left (mm) ***mean of the last 1 year before TART diagnosis NA: not available, BA: bone age, CA: chronological age, min: minimum, max: maksimum.*

Table 3. Comparison of follow-up ultrasound dimensions of TART with laboratory values

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
TART size at diagnosis (mm)	NA/NA	3	microlithiasis	14	13	5
TART size at last control (mm)	-	5	8	14	23	29
Follow-up time with US (years)	-	4.6	2	4.3	4.3	6
17-OHP level (ng/ml)*	1.3	16.9	19	0.87	37.3	37.2

**mean of the last 1 year before last USG, NA not available*

follow-up parameters were comparable between groups.

The characteristics of 6 patients are summarized in Table 2. TART was diagnosed after the onset of puberty in all patients expect one. Four patients (patients 2, 3, 4 and 6) received leuprolide acetate with the diagnosis of central precocious puberty before determination of TART.

While a unilateral lesion was detected in one of the patients, other patients had bilateral lesions. During the 4.5 year follow-up of the patient with unilateral TART, no lesion developed in the contralateral testicle.

MRI was performed in one patient (Case 6) to detect significant tumor growth, and to exclude malignancy. MRI showed hypointense lesions compatible with TART.

Mean follow-up time of the patients was 4.2±1.4 years. TART size increased during follow-up in four patients (Table 3).

DISCUSSION

The prevalence of TARTs in boys with CAH was 31.5% in the current study. Reported prevalence of TARTs varied between 14% to 86% in the literature.[1-11] This variation is related to age range of the patient

population, the severity of the disease and the method of detection. In studies included only children, the prevalence was reported between 10% to 70%.[8,10] TART prevalence was associated with the severity of the disease, and it was more common in patients with classic salt-wasting type CAH.[8,10] However, cases with simple virilising or non-classical forms of 21-hydroxylase or 11-hydroxylase deficiency have also been reported.[5,12-14] Most of the studies reported that, TART was associated with non-compliance to treatment or inadequate treatment.[5,8,12,15] However, TART was also described in well-controlled cases.[8,11,13,16,17] Therefore, metabolic control may not be the only factor contributing to the development of TART. In our case series, Case 1 had high ACTH levels, however other clinical and laboratory data were not suggestive of inadequate metabolic control. Cases 3 and 6 had high serum 17-OHP levels and precocious puberty suggestive of inadequate control. Cases 2 and 4 had normal mean ACTH and 17-OHP levels before diagnosis of TART, however both of them had a history of precocious puberty. Case 5 was well-controlled. As a conclusion, 4 of 6 TART patients had inadequate metabolic control.

In our study the median age of the patients at the time of the diagnosis of TART was 9.6 (5.25-12.41) years and the youngest patient was 5.25 years old. TARTs are reported to be more common in adolescence and postpubertal period, the youngest patient described in the literature was 1.8 years old.[8,11] There is no consensus about time to start screening for TARTs. An expert opinion suggests screening by testicular ultrasound assessments should begin in adolescence.[18] However, regarding prepubertal cases reported with TART, screening should be started earlier, especially in poorly controlled patients.

Eighty percent of TARTs are reportedly bilateral, and rarely unilateral.[10] Similar to reported incidence rates five of our cases (%83) had bilateral TART. Bilateralism of the lesions should be linked with the origin of TART. The etiopathology of TARTs has been related to their embryological development. It has been speculated that, TARTs develop from the embriyogenic pluripotent steroidogenic cell types that are already present in utero. Gonadal and adrenal cells originate from a common adrenogenital primordium, and during differentiation and migration of gonadal cells, undifferentiated adrenal cells may remain within testicular tissue.[1,19] In poorly controlled patients with CAH, high ACTH levels cause proliferation of undifferentiated adrenal cells which induces the formation of TART in rete testis.[3] Optimization of steroid treatment is recommended to prevent disease progression. However, suppression of ACTH secretion is not always successful in reducing tumor size, and even well-controlled CAH patients with normal or suppressed plasma ACTH levels have testicular adrenal resting tumors.[1,6,8] The pubertal LH peak and its trophic effect are predicted to contribute to tumor growth.[6,10] In our study, TART was diagnosed after onset of puberty in our five cases (83.3%). Four of the patients had central precocious puberty suggestive of poor hormonal control of CAH. Thus, a conclusion suggesting that the trophic effect of LH or high ACTH due to poor control caused TART can not be regarded.

Differentiation of TARTs from adrenal tumors like testicular Leydig cell tumors (LCT), adrenocortical adenomas should be done in case of clinical or radiological suspicion.[6,8] More than 90% of the cases with LCT are unilateral[8] Additionally, The presence of Reinke crystalloids has never been reported in TARTs, but sometimes they are seen in LCT. However, differential diagnosis is very difficult as these tumors share the same steroidogenic cells origin.[20,21]

Treatment of TARTs depends on the stage of the tumor. According to Claashen-van der Grinten et al.[7], TARTs are classified in five different stages. In Stage 1, there are adrenal rest cells within the rete testis, not detectable by scrotal testicular ultrasound. In Stage 2, these cells become hyperplastic and hypertrophic. Further growth of these cells will lead to the development of multilobular lesions and compress the seminiferous tubules (Stage 3). Focal lymphocytic infiltrate and peritubular fibrosis are detected in TART at Stage 4 and, chronic obstruction, irreversible damage of testicular parenchyma is detected at Stage 5. Therefore, it is important to detect and treat the tumours before permanent damage of the testis has occurred. High-dose glucocorticoid therapy to suppress ACTH was recommended in cases with Stages 2 and 3, however

this treatment was not always successful in reducing the lesion size. Temporary increase in tumor size has also been reported in some patients.[5,13] Different steroid formulations (hydrocortisone, dexamethasone and prednisone) have been used as treatment of TARTs, and the superiority of one over others has not been reported so far.[5,8,13,22] Testis-sparing surgery has been also used as a treatment option in Stages 3 and 4.[1,6,15,23,24] Successful testicular sparing surgery has been described in small groups of patients with TARTs, but no significant improvement in gonadal function after surgery was seen.[15,23] TARTs might reappear after surgery.[15,23] In our clinic, the treatment plan after detection of TART varies according to the patient's clinic, but generally includes increasing the dose of hydrocortisone or adding dexamethasone to the treatment according to patient's age. Treatment dose was not increased after the detection of TART in Case 1 due to good laboratory and clinic control markers. High ACTH levels were attributed to variation of blood sampling time and we did not want to make dose adjustment based on a laboratory assessment. In rest of the patients, treatment doses were increased. In Cases 5 and 6, dexamethasone was added to therapy. However, serum 17-OH-P levels remained high suggestive of non-compliance to therapy.

There are some limitations of our study. Although, we performed non-parametric tests to compare medians, statistical results may not be reliable due to small sample size.

As a result, although TARTs are seen more frequently in pubertal period and in poorly controlled patients with CAH in the literature, well-controlled and prepubertal cases may be encountered as in our study. Therefore, routine scrotal ultrasound control should be performed intermittently in childhood and adolescence in male patients with CAH.

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The Knowledge and Attitudes of Medical Students, Nurse Trainees, and Pediatric Patients' Caregivers About Influenza and Influenza Vaccination in Prepandemic Era

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ABSTRACT

Objective: *Influenza is a highly contagious respiratory infection influencing all aged people. Healthcare workers (HCWs) not only are vulnerable to influenza infection, but also act as a possible mediator for infection transmission. The best way to prevent influenza is annual vaccination. The aim of this study is to evaluate the knowledge and attitudes of medical students, nurse trainees, and pediatric patients' caregivers about influenza and influenza vaccination in our tertiary hospital.*

Methods: *We performed the study between April 01, 2019 and June 01, 2019. The survey consisted of a 22-item questionnaire that included questions about the demographic properties, vaccination status, decisions and attitudes about the influenza disease and influenza vaccination.*

Results: *Among 600 participants 502 of them completed the survey (response rate: 83%). One hundred and fifty participants from each group, who fully completed the questionnaires were included in the study. Most of the study participants have never get flu vaccination before (p<0.001). It was seen that the difference between common cold and flu was better known by medical students and nurse trainees, than the caregivers (p<0.001). A higher percentage of caregivers agreed with the decision that flu could not disappear without using antibiotics (26.0% vs 5.3% and 6.7%) (p<0.001). Most of the participants declared the thought of unnecessity of vaccination, as influenza is a simple infection (p=0.05). Approximately half of the medical students, 70% of the nurse trainees, versus 46% of the caregivers reported that to experience a disease itself is better than vaccination against it (p=0.007). A higher proportion of caregivers noted that they heard or read about harmful effects of influenza vaccines on internet or social media (p=0.008).*

Conclusion: *This study showed that most of the study participants did never get flu vaccination before. The difference between common cold and flu was better known by medical students and nurse trainees. A higher ratio of caregivers agreed that flu could not disappear without using antibiotics. Most of the participants declared the thought of unnecessity of vaccination. High percentage of participants had misinformation regarding influenza vaccines. A higher proportion of caregivers noted that they heard or read about harmful effects of influenza vaccines on internet or social media.*

INTRODUCTION

Influenza (flu) is a respiratory infection influencing all aged people, which is caused by influenza viruses. It is a highly contagious disease, which presents with a wide spectrum varying from mild symptoms to lethal conditions. It is estimated that annual epidemics result in about 3-5 million severe cases and 290,000-650,000 deaths from respiratory diseases, worldwide.[1] Turkish Health Ministry publishes territorial sentinel surveillance reports each week during the influenza season.[2] Fever, malaise, and cough are its most frequent symptoms. Risk groups, who are more prone to complications and mortality, consist of small children, elderly people, patients with underlying conditions, and healthcare workers

(HCWs). HCWs not only are vulnerable to influenza infection, but also act as possible mediators for infection transmission. In order to prevent influenza and its complications, the best way is annual vaccination. Hence, high coverage rate of vaccination plays a key role. Vaccination of HCWs has been recommended by CDC since 1981.[3] Vaccination of doctors and nurses and reasons for barriers of non-vaccination have been widely investigated until now[4-6] However, vaccine candidate HCWs, including medical students and nurse trainees had insufficient knowledge, about flu and flu vaccination. In addition, Turkish caregivers are under-evaluated, too. All of these groups have inevitably contact with patients and other risk groups during clinical rotations and hospital admissions. They should have responsibility and increased awareness about the disease and need for annual immunization against influenza.

In order to constitute a herd immunity against infectious diseases, HCWs and caregivers of children who are primarily responsible for care stand on the front row. However, there were hesitancies and refusals about vaccines with a rising trend for childhood influenza vaccination before the Covid-19 pandemic.[7] Generally, influenza is often confused with common cold and its real incidence and risks are underestimated. As a result, knowledge and perceptions about the influenza and its vaccines are not confidential. The rate of the vaccination is low in Turkey and all over the world.[8-10] Despite various facilities promoting vaccination carried out by both individual and governmental authorities, disinformation in the media, various social network sites, and influencers have a negative impact in vaccination coverage among HCWs, like the rest of the population.

The aim of this study is to evaluate the knowledge and attitude of medical students, nurse trainees, and pediatric patients' caregivers about influenza and influenza vaccination in prepandemic era in our tertiary hospital.

MATERIAL and METHODS

We performed this study in Adnan Menderes University Hospital between April 01, 2019 and June 01, 2019. The survey consisted of a 22-item questionnaire based on available similar literature. Every participants filled out the questionnaires themselves. The survey included questions about the demographic properties, vaccination status, decisions and attitudes about the influenza disease and influenza vaccination.

The participants answered all questions with 5-point Likert scale [(1)Strongly disagree; (2)Disagree; (3) Neither agree nor disagree; (4)Agree; (5)strongly agree)]. During the analyses, we combined points 1 and 2, while combining points 3, 4, and 5.

The data were analyzed by descriptive statistics using SPSS (Statistical Package for the Social Sciences) version 17.0 software. We calculated mean and standard deviation for measurable variables and percentage and frequency of occurrence for qualitative features. We made comparison analyses by means of the chi-square test and One Way ANOVA-post hoc-Scheffe alpha tests. Statistical significance was set at 0.05.

RESULTS

Among 600 participants, 502 of them completed the survey (response rate: 83%). One hundred and fifty participants from each group, who fully completed the questionnaires, were included in the study. We discarded incompletely responded questionnaires. The mean age of the participants were as follows; medical students, 21.3±1.4; nurse trainees 18.6±1.4; and patients' relatives, 37.1±12.4 years. The mean age of the caregivers was statistically significantly higher (<0.001) (Table 1). Female gender predominance was seen in the study population (p=0.04). Education status of majority of the caregivers was elementary school, while the others were mostly high school graduates (p<0.001). Most of the study participants have never had flu vaccination before (p<0.001).

Influenza disease

It was seen that the difference between common cold and flu was better known by medical students and nurse trainees, rather than caregivers (p<0.001) (Table 2). Although, majority of the participants did not agree with the decision that flu cannot disappear without using antibiotics, a higher percentage of

Table 1. Demographic properties of the study population, n (%)

	Medical students (n=150)	Nurse trainees (n=150)	Caregivers (n=150)	p
Gender				
Female	80 (53.3%)	73 (48.7%)	94 (62.7%)	**0.04**
Male	70 (46.7%)	77 (51.3%)	56 (37.6%)	
Education status				
Elementary	0 (0%)	0 (0%)	60 (40.0%)	**<0.001**
High school	140 (93.3%)	150 (100%)	51 (34.0%)	
University	10 (6.7%)	0 (0%)	39 (26.0%)	
Flu vaccination status				
Never	89 (59.3%)	64(42.7%)	94 (62.7%)	**<0.001**
Once	31 (20.7%)	34 (22.7%)	33 (22.0%)	
More than once	27 (18.0%)	51 (34.0%)	14 (9.3%)	
Every year	3 (2.0%)	1 (0.7%)	9 (6.0%)	

Table 2. The evaluation of knowledge and attitudes of study population with respect to influenza disease, n (%)

	Medical students (n=150)	Nurse trainees (n=150)	Caregivers (n=150)	p
Flu and common cold are the same				
Agree	9 (6.0%)	15 (10.0%)	52 (34.7%)	**<0.001**
Disagree	141 (94.0%)	135 (90.0%)	98 (65.3%)	
Flu cannot disappear without antibiotics				
Agree	8 (5.3%)	10 (6.7%)	39 (26.0%)	**<0.001**
Disagree	142 (94.7%)	140 (93.3%)	111 (74.0%)	
As influenza is a simple infection, there is no need of vaccination				
Agree	18 (12.0%)	27 (18.0%)	34 (22.7%)	**0.05**
Disagree	132 (88.0%)	123 (82.0%)	116 (77.3%)	
It is better to experience a disease itself, rather than vaccination				
Agree	74 (49.4%)	105 (70.3%)	69 (46.2%)	**0.007**
Disagree	76 (50.6%)	45 (29.7%)	81 (53.8%)	

caregivers agreed with this decision (26.0% vs 5.3% and 6.7%) (p<0.001). Most of the participants declared the thought of unnecessity of vaccination, as influenza is a simple infection (p=0.05). Approximately half of the medical students, 70% of the nurse trainees, against 46% of the caregivers reportedly decided that experience a disease itself was better than vaccination against them (p=0.007).

Influenza vaccine

The majority of the medical students (92.7%) and nurse trainees (94.7%) but only approximately half of the caregivers reported that they had known that influenza vaccines contained attenuated microbes, (p<0.001). Among all study groups, higher proportion of caregivers (85.0% vs. 61.3% and 60.0%) thought that influenza vaccines contained vitamins and minerals and influenza vaccines were curative (p=0.002 and p<0.001). Similarly, a higher proportion of caregivers noted that they had heard or read about harmful effects of influenza vaccines on internet or social media (p=0.008). Majority of the study population reported that they had known the risk groups for influenza vaccination. However comparatively higher percentage of medical students had this information (95.3% vs. 87.3% and 73.3%) (p<0.001).

Table 3. The evaluation of knowledge and attitudes of study population with respect to influenza vaccines and vaccination

	Medical students (n=150)	Nurse trainees (n=150)	Caregivers (n=150)	p
Influenza vaccines include attenuated microbes				
Agree	139 (92.7%)	142 (94.7%)	74 (49.3%)	**<0.001**
Disagree	11 (7.3%)	8 (5.3%)	76 (50.7%)	
Influenza vaccines include vitamins and minerals				
Agree	58 (38.7%)	60 (40.0%)	85 (56.7%)	**0.002**
Disagree	92 (61.3%)	90 (60.0%)	65 (85.0%)	
Influenza vaccines are curative				
Agree	15 (10.0%)	19 (12.7%)	79 (52.7%)	**<0.001**
Disagree	135 (90.0%)	131 (87.3%)	71 (47.3%)	
Influenza vaccines prevents disease				
Agree	129 (86.0%)	121 (80.7%)	119 (79.3%)	0.28
Disagree	21 (14.0%)	29 (19.3%)	31 (20.7%)	
Know the place to get influenza vaccine shot				
Agree	120 (80.0%)	110 (73.3%)	117 (78.0%)	0.37
Disagree	30 (20.0%)	40 (26.7%)	33 (22.0%)	
Prevent him/her-self and family against influenza if get vaccinated				
Agree	95 (63.3%)	78 (52.0%)	84 (56.0%)	0.13
Disagree	55 (36.7%)	72 (48.0%)	66 (44.0%)	
Should get influenza vaccine annually				
Agree	47 (31.3%)	45 (30.0%)	53 (35.3%)	0.58
Disagree	103 (68.7%)	105 (70.0%)	97 (64.7%)	
No doctor advised me influenza vaccination				
Agree	103 (68.5%)	98 (65.2%)	105 (70.3%)	0.78
Disagree	47(31.5%)	52 (34.8%)	45 (29.7%)	
Heard/read about harmful effects of influenza vaccines on internet/social media				
Agree	15 (10.0%)	33 (21.9%)	43 (28.6%)	**0.008**
Disagree	135 (90.0%)	117 (78.1%)	107 (71.4%)	
Do not think influenza vaccines are useful				
Agree	32 (21.3%)	30 (20.0%)	43 (28.6%)	0.39
Disagree	118 (78.7%)	120 (80.0%)	107 (71.4%)	
Did not have influenza shot because of fear of needle phobia				
Agree	10 (6.7%)	21 (14.1%)	23 (15.4%)	0.16
Disagree	140 (93.3%)	129 (85.9%)	127 (84.6%)	
Would vaccinate regularly if influenza vaccine was free of charge				
Agree	30 (20.0%)	21 (14.1%)	30 (20.0%)	0.51
Disagree	120 (80.0%)	129 (85.9%)	120 (80.0%)	
Know the risk groups for influenza vaccination				
Agree	143 (95.3%)	131 (87.3%)	110 (73.3%)	**<0.001**
Disagree	7 (4.7%)	19 (12.7%)	40 (26.7%)	

DISCUSSION

Vaccine subtypes are analyzed and changed annually according to the worldwide trends. Despite advice of health authorities regarding annual vaccination, only a small percentage of the study population declared that they got regularly vaccinated each year. Dramatically, most of the participants reported to have never got flu vaccination before. A multicenter survey including all medical faculties revealed that 59% of Turkish medical students have never got influenza vaccination.[11] In the study of Oguz MM[12], after introduction and elucidating the characteristic features of the flu vaccine, coverage rate was shown to increase from 10.8% to 39.9% in the next season. Among students in all grades of medical education including freshmen and students training in medical and healthcare-related faculties were reported to have higher vaccination coverage than the others.[13] However, a comparison was not performed between the students with respect to their academic years in this study. Influenza vaccination rates are known to be quite low among Turkish HCWs. Incorrect knowledge and attitudes about the vaccine and disease are the most important reasons to decline vaccination. In a multicenter study, it was reported that 6.7% of the HCWs were regularly vaccinated each year and that 55% of them had never had the influenza vaccine before similar to the result of this study.[14] Even vaccination campaigns could not achieve a significant increase.[15] In another survey, only 41.6% of Turkish HCWs chose the correct answer indicating the necessity of annual flu vaccination.[16] Females predominance, for which mostly caregivers contributed, was seen in this study population, similar to other studies.[5,15] Education status of majority of the caregivers was elementary school, while the others graduated mostly from a high school. However, education level does not always have a significant effect on the likelihood of being vaccinated among HCWs.[17] A systematic review stated that sociodemographic variables such as gender and age were the most reported, but also the most inconsistent predictors of influenza vaccination.[4]

There may be some doubts and lack of knowledge of HCWs about the severity of influenza disease and the effectiveness of the vaccine, especially when HCWs are new to the clinical practice. In the study by Erbay et al.[15] it was stated that the reason for non-vaccination among the HCWs was mostly related to the thought of insufficient protection of the vaccines. In addition, the doctors added that ignoring the importance was another reason for non-vaccination. In this study, most of the participants entertained the thought of unnecessity of vaccination, as influenza is a simple infection. Similarly, in a previous study, 21.8% of medical doctors reported that they found influenza vaccines unnecessary.[15] The responders including caregivers in the study by Adadan Güvenç et al.[9] did not believe that vaccination protected people in close surroundings. The caregivers' belief in effectiveness of influenza vaccines was found as a strong predictor for vaccination of high-risk children against influenza.[18]

It was seen in this study that the difference between common cold and flu was better known by medical students and nurse trainees, rather than caregivers. The 34.7% of caregivers in this study agreed that flu and common cold were the same disease. In the survey of Adadan Güvenç et al.[9], 20.9% of the patients and their relatives above 18 years of age did not know the right answer to this question. Although, majority of the participants in our study did not agree with the decision that flu could not disappear without using antibiotics, a higher percentage of caregivers agreed with this decision (26.0% vs 5.3% and 6.7%). In a previous report, 44.4% of Turkish adult patients and their caregivers reported that flu could not be treated without antibiotics.[9] Fear of getting ill due to vaccine or its side effects can interfere with the vaccine coverage. Approximately half of the medical students, 70% of the nurse trainees, versus 46% of the caregivers in this study reported that they decided that to experience a disease itself was better than getting vaccinated against it. Differently, a recent, multicenter national survey in our country revealed that getting the vaccine in order not to catch influenza ranked first among the reasons why HCW responders got influenza vaccine.[14]

The majority of the medical students and nurse trainees, while approximately half of the caregivers, reported to know that influenza vaccines contained attenuated microbes. Moreover, in this study

among all study groups, most of the participants declared their opinions indicating that influenza vaccines contained vitamins and minerals. In the literature, one of most important barrier to vaccinations has been reported as lack of information.[19] Anti-vaccination trend has started to become a big challenge before the Covid-19 pandemic, especially among the caregivers of children and these movements against vaccination take a large place especially in social media.

A higher proportion of caregivers noted that they had heard or read about harmful effects of influenza vaccines on internet or social media. In a Greek survey, public information about flu vaccines was cited as a major reason for refraining from getting vaccinated.[20] In a previous report, doctors who were not vaccinated against influenza declared that they thought of the presence of probable unknown, or neurological, or local side effects.[15] Also in a previous report 31.1% of Turkish HCWs reported that they had believed that seasonal flu vaccines decreased body resistance.[16] Majority of relatives of patients in a previous Turkish study declared that vaccines could cause flu and had serious side effects.[1] In our study, majority of the study population reported that they had known the risk groups for influenza vaccination. Although each risk category was not specified in this study, subjects with diseases of the hematopoietic organs or chronic circulatory, respiratory, or renal conditions, cohabitants of at-risk subjects, and people over 65 years of age were the mostly reported risk groups by the HCW responders in the study by Arghittu et al.[6]

While interpreting the results of this study, some limitations should be considered. This study was conducted in our tertiary care hospital in Turkey. As a result, the results may not be generalizable for all parts of Turkey. Anyway, number of the participants in the population is not low, and statistically important findings will be beneficial to review the knowledge and attitude of this population. Although there is a risk of lower response rates and unresponsiveness, a qualitative study might have allowed a deeper understanding of the knowledge and attitude towards determining the decision to vaccinate, which would help for improvements in more areas. However, our survey was also useful when considering issues of time and cost.

As a conclusion, vaccination of HCWs continues to be a priority and vaccine uptake should be improved. This study showed that most of the study participants has never get flu vaccination before. The difference between common cold and flu was better known by medical students and nurse trainees. A higher percentage of caregivers agreed that flu cannot disappear without using antibiotics. Most of the participants declared the thought of unnecessity of vaccination, as influenza is a simple infection. High percentage of participants had misinformation regarding influenza vaccines. A higher proportion of caregivers noted that they had heard or read about harmful effects of influenza vaccines on internet or social media. In addition to an attempt to increase the level of knowledge of the physicians, multidirectional trainings targeting to change the attitude and behaviors of the HCWs and caregivers towards influenza vaccination should be applied in prevention of influenza.

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Comparison Between Celiac Patients and Healthy Control Group Regarding Vitamin-Mineral Levels and Complete Blood Count Parameters

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ABSTRACT

Objective: *We aimed to compare the mean platelet volume (MPV) and plateletcrit (PCT) and vitamin-mineral levels in pediatric celiac disease patients with the healthy control group and to compare the results with the literature.*
Methods: *In this study, clinical and laboratory data of 80 pediatric patients diagnosed with celiac disease (CD) between July 2017 and December 2018 and 42 healthy children in the same age group were retrospectively analyzed.*
Results: *There was no significant difference between the groups in terms of age and gender (p=0.383, and p=0.462, respectively). The frequency of anemia, folate, iron and vitamin D deficiencies was higher in celiac patients compared to the control group (p=0.001, p=0.027, p<0.001, and p<0.001, respectively). When the patients were evaluated according to their complete blood count and vitamin-mineral levels; hemoglobin (Hb), mean corpuscular volume (MCV), ferritin and vitamin D levels were found to be significantly lower in the CD group compared to the control group (p<0.001, p=0.026, p<0.00, and p=0.001, respectively). Platelet (PLT), PCT, MPV levels were found to be significantly higher in the CD group compared to the control group (p=0.010, p<0.001, and p<0.001, respectively). We found a weakly negative correlation between the vitamin D levels and the degree of the Marsh classification (r: -0.273, and p=0.023).*
Conclusion: *Our study have shown that MPV, PCT values are higher and Hb, folate, iron and vitamin D levels are lower in patients with CD compared to healthy controls. We recommend investigating other nutrient deficiencies besides iron deficiency, especially in treatment-resistant anemias. We think that the correlation between vitamin D levels and the degree of histological damage should be elucidated with larger-scale and more comprehensive studies.*

INTRODUCTION

Celiac disease (CD) is an autoimmune disease that develops against gluten found in foods such as barley, wheat and rye in genetically susceptible individuals. The main underlying pathology of this disease is inflammation in the small intestine. Mean platelet volume (MPV) was investigated as an inflammatory marker in diseases such as inflammatory bowel disease and acute pancreatitis.[1,2] Some studies have stated that there is a negative correlation between MPV and inflammatory activity, while others have suggested a positive relationship between increased MPV and disease severity.[3] Purnak et al.[3] emphasized that high MPV values in CD patients may be an indicator of intestinal inflammation, and also, it can be a useful marker to follow diet compliance of patients at a lower cost. It has been shown that the major inflammatory cytokine that is increased in celiac patients is IL-6.[4] It is thought that IL-6 may stimulate megakaryocyte ploidy, leading to more reactive, increased platelet

production and increase in MPV values.[5] There is currently no study showing the change in the plateletcrit (PCT) value in the case of this reagent triggered by IL-6 and increased platelet production in celiac patients. For this reason, we aimed to compare MPV and PCT and vitamin-mineral levels in the pediatric CD patients at the time of diagnosis with a healthy control group and to compare our results with the literature.

MATERIAL and METHOD

In this study, clinical and laboratory data of 80 pediatric patients diagnosed with CD and 42 healthy children of the same age group between July 2017 and December 2018 were retrospectively analyzed.

The study was conducted in accordance with the Principles of Declaration of Helsinki. Before starting the study, approval was obtained from the ethics committee of an education and research hospital and a tertiary university-affiliated hospital (date: 10.24.2018; session: 2018/19; protocol No: 418.

The diagnosis of celiac disease was made in line with the recommendations contained in the guideline of European Association of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) published in 2012.[6]

Exclusion criteria

Patients with hypertension, hypercholesterolemia, hypertriglyceridemia, obesity, acute coronary syndrome, heart failure, cancer, hematological diseases, diabetes, liver failure, renal failure, acute or chronic infection were not included in the study.

Evaluation of nutritional status

In children less than 2 years of age, height was measured with the aid of an infantometer with the children placed in a supine position on a flat surface. Their head and knees were fixed by a second person. Children older than two years of age were measured with socks and shoes removed and using a vertical portable stadiometer calibrated to the nearest millimeter. Participants' weights were measured with a digital electronic scale calibrated to the nearest decimal fraction of one kilogram. Weight Z score, height Z score, body mass index (BMI) Z score for age and gender were calculated using World Health Organization (WHO) data. Patients with any of the parameters of body weight, height and BMI Z score below -2 were considered undernourished.

Evaluation of laboratory data

Iron deficiency: ferritin <30 ng/mL[7]
Folate deficiency: folate <4 ng/mL[8]
Vitamin B12 deficiency: vitamin B12: <200 pg/mL[9]
Vitamin D deficiency: vitamin D: <20 ng/mL[10]
Anemia: A lower than normal level of hemoglobin for age and gender.

Statistical analyses

Statistical Package for the Social Sciences for Windows (SPSS Inc., Chicago) 22 software package was used for statistical analysis. Study variables were presented as number (n) - percentage (%), mean ± standard deviation. The normal distribution of variables was tested using the Kolmogrov- Smirnov test. Normally distributed parameters were evaluated by one-way analysis of variance (ANOVA) or Student's t test; Kruskal- Wallis or Mann- Whitney U test was used for numerical variables that did not show normal distribution. Student's t test, Mann-Whitney U test or chi-square test were used to evaluate statistical significance.

Correlation analysis was performed to determine whether there was a linear relationship between the two numerical measurements and to show the direction and severity of this relationship. For data with normal and non-normal distribution, use of Pearson correlation coefficient, and Spearman Rank correlation coefficient was preferred, respectively. A p value of less than 0.05 was considered statistically significant.

RESULTS

The mean age of the patients was 8.68±5.16 years in the control group and 9.51±4.76 years in the CD group. There was no statistically significant difference between the groups in terms of age and gender (p=0.383, and p=0.462, respectively) (Table 1).

When the patients were evaluated according to their anthropometric measurements, weight, height and BMI z scores in CD were found to be significantly

lower than the control group (p <0.001). Malnutrition was not observed in the control group, while it was detected in 29 patients (36.3%) in the CD group. This intergroup difference was statistically significant (p<0.001) (Table 1).

We detected anemia in 2 patients (4.8%) in the control and 24 patients (30%) in the CD group. Vitamin B12 deficiency was seen in 8 patients (12.7%) in the CD group and 1 patient (2.4%) in the control group. While folate deficiency was seen in 7 patients (11.1%) in the CD group, there was no folate deficiency in the control group. Iron deficiency was seen in 53 patients (66.3%) in the CD and in 20 patients (47.6%) in the control group. Vitamin D deficiency was seen in 41 patients (59.4%) in the CD and in 9 patients (21.4%) in the control group. The frequency of anemia, folate, iron and vitamin D deficiency was higher in the CD group compared to the control group (p=0.001, p=0.027, p<0.001, and p <0.001, respectively). Although frequency of vitamin B12 deficiency was higher in the CD group, this increase was not statistically significant (p=0.064) (Table 1).

When the patients were evaluated according to their complete blood counts and vitamin-mineral levels; hemoglobin (Hb), mean corpuscular volume (MCV), ferritin and vitamin D levels were found to be significantly lower in the CD group compared to the control group (p<0.001, p=0.026, p<0.00, and p=0.001, respectively). Platelet (PLT), plateletcrit (PCT), and mean platelet volume (MPV) levels were significantly higher in the CD group compared to the control group (p=0.010, p<0.001, and p<0.001, respectively). There was no significant difference between the two groups in terms of white blood cell (WBC) counts, mean corpuscular hemoglobin (MCH), Mentzer Index, vitamin B12 and folate levels (p=0.399, p=0.705, p=0.647, respectively, p=0.833, and p=0.131) (Table 2).

When the correlation between the degree of pathological Marsh classification and hematological parameters and vitamin-mineral levels in celiac patients was evaluated, there was no significant correlation between Hb, MPV, PCT, vitamin B12 and folate levels and the degree of Marsh classification. However, we found a weakly negative correlation between vitamin D level and the degree of the Marsh classification (r: -0.273, p=0.023).

DISCUSSION

This study is one of the rare studies evaluating

Table 1. Comparison of the groups based on anthropometric measurements, demographic characteristics and vitamin-mineral deficiencies

	Control (n=42) Mean±SD	CD (n=80) Mean±SD	p*
Age	8.68±5.16	9.51±4.76	0.383
Weight Z score	0.13±0.84	-1.09±1.57	<0.001
Height Z score	0.23±1.08	-0.83±1.51	<0.001
BMI Z skor	-0.05±0.86	-0.89±1.23	<0.001
	n (%)	**n (%)**	**p****
Gender			
Female	25 (59.5%)	53 (66.3%)	0.462
Male	17 (40.5%)	27 (33.8%)	
Malnutrition	0 (0%)	29 (36.3%)	<0.001
Anemia	2 (4.8%)	24 (30%)	0.001
Vitamin B12 deficiency	1 (2.4%)	8 (12.7%)	0.064
Folate deficiency	0 (0%)	7 (11.1%)	0.027
İron deficiency	20 (47.6%)	54 (80.6%)	<0.001
Vitamin D deficiency	9 (21.4%)	41 (59.4%)	<0.001

*Statistics: *Independent Student T test, **Crosstabs-chi-square*
BMI: body mass index; CD: celiac disease; SD: standard deviation

Tablo 2. Comparison of complete blood count parameters according to groups, mean±SD

	Control (n=42) Mean±SD	CD (n=80) Mean±SD	p*
WBC (x10^3 cells/uL)	7.93±2.18	8.44±3.51	0.399
Hb (g/dL)	13.26±1.67	11.74±1.65	<0.001
PLT (x10^3 cells/uL)	303.59±93.84	361.56±125.81	0.010
PCT (%)	0.28±0.08	0.35±0.08	<0.001
MPV (fL)	9.72±0.69	10.30±0.89	<0.001
MCH (pg)	25.15±4.61	24.52±3.05	0.705
MCV (fL)	77.90±5.07	75.25±7.75	0.026
Mentzer Index	15.95±1.82	15.77±1.97	0.647
B12 (pg/mL)	362.14±185.87	371.06±228.27	0.833
Folate (ng/mL)	9.80±4.09	8.43±4.68	0.131
Ferritin (ng/mL)	34.49±20.89	17.89±24.34	<0.001
Vitamin D (ng/mL)	25.22±9.16	18.73±10.08	0.001

*Statistics: *Independent Student T test*
SD: standard deviation; CD: celiac disease; WBC: white blood cell; Hb: hemoglobin; PLT: platelet; PCT: plateletcrit; MPV: mean platelet volume; MCH: mean corpuscular volume

hematological parameters and vitamin-mineral levels in detail between CD and healthy children. Wierdsma et al.[11] reported folate deficiency in 20%, vitamin B12 deficiency in 19%, and ferritin deficiency in 46% of their CD patients. Other studies have found folate deficiency approximately in 11-12%, vitamin B12 deficiency in 8-41%, iron deficiency in 8-93% of their CD patients.[12-14] In our study, we found that the rates of folate, B12 and iron deficiencies were compatible with the literature data.

The prevalence of iron deficiency anemia (IDA) in CD is quite variable in different geographical regions and different age groups. It is lower in developed countries (5-40%) than in developing countries (>80%).[15,16] The prevalence rates of anemia in CD have been reported as (93.2%) in an Indian study, 21.6% in a European study, 8-40% in the American cohorts, and 50% in the Middle East and North Africa population.[12,17-20]

In our study, we found the prevalence of anemia similar to the rates of developed countries. This rate (30%) was significantly higher than the control group patients. The main mechanism of IDA in celiac disease is malabsorption. Iron deficiency is not the only factor that causes anemia in CD. Vitamin B12 and folic acid deficiencies can also cause megaloblastic anemia, which can increase the severity of anemia. In the study of Berry et al.[12], it was emphasized that mixed nutrient deficiencies (vitamin B12, folate, iron, vitamin B6, zinc, and vitamin A) can increase the frequency of anemia. In our study, zinc, vitamin A, and vitamin B6 were not measured in any patient. However, indicated number of patients had iron (n=2: 2.5%), folate and vitamin B12 deficiency (n=6: 7.5%), folate and iron deficiency (n=6: 7.5%), vitamin B12 and iron deficiency (n=7: 8.75%). For this reason, we recommend investigating other nutrient deficiencies in the presence of anemia that does not improve despite iron supplementation, as mentioned in the literature.

Recent studies have emphasized that as the severity of villous atrophy and anti-tissue transglutaminase (DTG) levels increase, the frequency of anemia and resistance to treatment are higher.[12,21,22] In our study, we did not find a significant correlation between the degree of villous atrophy and DTG levels and ferritin, vitamin B12 and folate levels. However, unlike the literature, we found a weakly negative correlation between vitamin D levels and the degree of villous atrophy (r: -0.273, p=0.023). We did not have any information about the diet and its nutrient content of these patients before the diagnosis of CD. Therefore, the data we found different from the literature may be due to differences in dietary intake and duration of exposure to sunlight.

As far as we know, a weakly significant negative correlation between the vitamin D level we found in our study and the severity of villous atrophy has not been emphasized in any previous study. Tanpowpong and Camargo[23] (suggested that vitamin D deficiency

at an early age may play an important role in childhood-onset (<15 years) celiac disease. Vitamin D deficiency may cause an irregular intestinal immune response in genetically susceptible individuals with increased disruption of the intestinal epithelial barrier as a result of the immune response to gluten and microorganisms. This impaired immune response can result in increased susceptibility to acute gastrointestinal infection. It has been emphasized that these mechanisms may pave the way for the development of celiac disease that begins in childhood.[24] Vitamin D is known to play an important role in bone health and regulation of the immune system. Low levels of bone mineral density (BMD) have been reported in children with CD.[24] Additionally, ACG, BSG and NASPGHAN, Italian Pediatric Societies also recommend evaluation of vitamin D status in CD.[25-28] Vitamin D supplementation during an intake of a gluten-free diet has been shown to prevent further bone loss, improve symptoms associated with osteomalacia, and normalize calcium levels.[29] In their study Ahlawat et al.[30] emphasized that vitamin D levels were higher in CD patients compared to the control group, but it was observed that the vitamin D ratios that CD patients took from milk, milk products and multivitamin preparations were similarly high. They associated this condiiton with the excess of estimated vitamin D intake rates. In our study, as in many other studies,[31-34] we found that vitamin D levels were significantly lower in patients with CD compared with the control group (p=0.001) (Table 2).

Another important finding of our study is that we detected higher MPV and PCT values in the CD group compared to the control group. Although the relationship between MPV and CD has been emphasized in several studies in the literature, ours is the only study that evaluates the PCT and MPV values in combination in CD and compares them with the control group. In the literature, MPV levels have been the subject of research in diseases such as myocardial infarction, stroke, diabetes, ulcerative colitis, chronic hepatitis B and acute pancreatitis. It has been emphasized that there may be a relationship between disease severity and MPV. In the first study about the relationship between CD and MPV, higher MPV values were reported in patients with CD.[35] In another study, it was reported that MPV increased in newly diagnosed CD patients compared to healthy controls, and these mean MPV values became normal over time in patients who followed the diet. Even MPV has been suggested to be used as a biomarker in the assessment of dietary compliance.[3] Although we could investigate the relationship between MPV,PCT and dietary compliance in CD in our study, high levels of PCT and MPV in CD patients seem to be compatible with other studies. Golwala et al.[36] stated that MPV and PCT levels could be predictors of mortality and accurately predicted 65% - 67% of related deaths. In another study, it was reported that PCT values were significantly higher in severe preeclampsia cases compared to mild preeclampsia cases. Ours is the only study comparing the relationship between CD and PCT relative to healthy controls. We found that PCT and PLT values were significantly higher in CD patients compared to the healthy control group. However, there was no significant correlation between PLT and PCT levels and serological findings and severity of histological damage in CD. Prospective randomized controlled large series are needed for a more reliable and detailed analysis of this relationship.

One limitation of our study is that our study was a retrospective study, so the retrospective nutritional history of the patients and the rate of exposure to sunlight were not known. Besides, the data were not re-evaluated after intake of a gluten-free diet, and the data concerning the presence of diseases such as megaloblastic anemia and chronic disease anemia that may accompany iron deficiency were not available. In addition, the fact that ours is a rare study comparing MPV, PCT values detected in CD patients and healthy controls and it is the only study showing a negative correlation between vitamin D levels and the degree of Marsh classification makes this article valuable.

In conclusion, our study shows that MPV, PCT values are higher and Hb, folate, iron and vitamin D levels are lower in CD patients compared to healthy children. In addition, we think that mixed vitamin-mineral deficiencies may coexist in CD patients, therefore, other nutrient deficiencies should be investigated in addition to iron deficiency in treatment-resistant anemias. We have found a negative correlation between vitamin D levels and

the degree of histological damage which requires conduction of more comprehensive studies.

Ethics Committee Approval: Approval was obtained from Kahramanmaras Sutcu Imam University Faculty of Medicine Clinical Research Ethics Committee (24.10.2018/10).

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An Evaluation of Pediatric Intensive Care Unit Infection Rates and Various Risk Factors

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ABSTRACT

Objective: *The pediatric intensive care unit (PICU) is a unit in which the general condition and vital signs of patients aged one month to 18 years are continuously monitored, and support treatments after advanced pediatric and surgical procedures are provided. Healthcare-associated infections (HAIs) can develop during some interventions and treatments. The purpose of this study was to investigate infection and handwashing rates for the previous five years in a hospital PICU providing tertiary intensive care and to examine HAI agent microorganisms and their resistance rates.*

Methods: *Data for patients followed-up at the Aydın Adnan Menderes University Hospital PICU between 1 January 2015, and 30 October 2020, were examined retrospectively. The study data were obtained from the hospital microbiology laboratory culture specimen results, radiology data, clinical visits, and information recorded on the National Healthcare-Associated Infections Surveillance System. HAIs rates, density, infectious agents and resistance rates, and hand hygiene compliance rates were calculated from these data.*

Results: *Two hundred and thirty-three patients were included in the study. The mean annual number of patient days was 1742±322. The mean annual total number of infections was 9.0±3.9, the mean infection rate was 4.2±2.8, and the mean infection density was 5.0±1.5. Bloodstream infections constituted the most common infections, followed by ventilator-associated pneumonia (VAP). Carbapenem resistance at a rate of 50% was determined for both Acinetobacter spp. and Pseudomonas aeruginosa. A strong correlation was determined between VAP and patient days (p=0.05, r=0.80). Hand hygiene observations revealed compliance rates of 48.1±14.3 in nurses, 33.9±28.2 in patient carers, 31.8±12.5 in physicians, and 30.9±26.2 in cleaning personnel.*

Conclusion: *Mean annual infection numbers in this study were similar to those of previous studies from other centers. The most common infection was bloodstream infections. Nurses had the highest handwashing rates, with physicians in the third place. Higher VAP was correlated with increased patient days.*

INTRODUCTION

The pediatric intensive care unit (PICU) is a unit in which patients aged from one month to 18 years are observed, basic vital signs can be monitored, support treatments such as fluid and blood transfusion, hemodialysis, resuscitation, and mechanical ventilation, can be provided, and advanced pediatric, some surgical, and diagnostic procedures can be carried out. Complications in PICU include healthcare-associated infections (HAIs) which constitute infections that are not present or incubating during admission to the health institution but develop after the third day of hospitalization.[1]

The general rate of HAI development in intensive care units is 20-40 percent, the most commonly reported being bloodstream infections (BSIs), ventilator-associated pneumonia (VAP), urinary tract infections (URTIs), and surgical site infections (SSIs).[2] The HAI rate in pediatric intensive care units (PICUs) is 6-12 percent. The microorganisms identified vary

depending on the type of infection. The most commonly isolated microorganisms include *Staphylococcus aureus*, coagulase-negative *staphylococci, enterococci* and *Candida* spp in BSIs, gram-negative bacteria, particularly *Pseudomonas aeruginosa,* in VAP, and *Escherichia coli, Klebsiella pneumoniae, Enterobacter* and *Candida* spp in URTIs. Rotavirus and respiratory syncytial virus are also infectious agents frequently seen in children. Treatment for microorganisms with high antibiotic resistance is limited, and mortality rates are high. Resistant microorganisms seen with increasing frequency, particularly in HAIs, include methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant coagulase-negative *staphylococci* (MRCNS), vancomycin-resistant *enterococci* (VRE), extended-spectrum beta-lactamases (ESBL)-positive *Klebsiella* and *E. coli*, and carbapenem-resistant *Pseudomonas* and *Acinetobacter*.[3] Risk factors for HAIs developing with these microorganisms include chronic diseases, sedative medication use, surgery, invasive interventions and procedures such as fluid and blood transfusions, intravenous nutrition, presence of nasogastric, central/urinary catheters, and mechanical ventilation.[2] Other risk factors are premature birth, low birth weight, congenital anomalies, and immunosuppression.[3]

Hand hygiene is the most important precaution against transmission of microorganisms in hospital. This low-cost and simple precaution has been described as capable of preventing half of nosocomial infections.[19] Low compliance with hand hygiene leads to the emergence of new and different microorganisms by affecting the hospital flora, and to an increase in nosocomial infections.[14] International guidelines recommend ensuring hand hygiene with frequent washing with soap and water and rubbing the hands with alcohol-based hand disinfectant. When hand hygiene is at a high level, the incidence of HAI is known to be low, and there is a decreased risk of microorganism transmission. However, research into epidemics has noted that compliance is low.[5]

The purpose of the present study was to examine infection and handwashing rates over the previous five years in a PICU providing tertiary intensive care service in our hospital, together with microorganism HAI agents and resistance rates.

MATERIAL and METHOD

Data for patients followed-up in the Aydın Adnan Menderes University Hospital PICU, Turkey, between 1 January, 2015, and 30 October, 2020, were evaluated retrospectively. The PICU operates continuously and without interruption as a third level, six-bed capacity, intensive care unit. The study data were collected through active and continuous surveillance by an infection control nurse (ECN). Patients' clinical manifestations, culture specimen results, radiology data, and clinical visits have been monitored in surveillance studies. Bacterial growth in patients' specimens and sensitivity results were monitored on a daily basis through transfer of data from the hospital microbiology laboratory to the hospital data management system. Data described in line with the diagnostic criteria set out in the National Health Service-Associated Infections Surveillance System, and recorded onto the system by ECN used in the present study.[1]

Handwashing observations were performed by ECN based on criteria specified in the World Alliance for Patient Safety Guideline for Observers at three-monthly periods for all physicians, nurses, patient carers, and cleaning personnel working in the unit.[1] Observation data were also obtained from information recorded in the National Health Service-Associated Infections Surveillance System hand hygiene section.

HAIs constitute infections that are not present or incubating during admission to the health institution and that develop after the third day of hospitalization and in association with health services.[1] Health-care worker occupation-related infections and those producing symptoms after discharge are also included in this class.

- Infection rate is calculated as number of infections/number of hospitalized patients x 100.
- Infection density is calculated as number of infections/patient days x 1000.
- The term patient days is defined as the length of the patient's stay in the unit in days.

Statistical analyses were performed on SPSS (Statistical package for the Social Sciences) version 17.0 software. Normality of distribution of variables was evaluated using the Kolmogorov-Smirnov / Shapiro-Wilk tests. Descriptive statistics were expressed as mean±standard deviation for normally distributed variables and as median (minimum-maximum) for non-normally distributed variables. Categorical variables were expressed as percentages (%). Correlation analyses were performed using Pearson's correlation test.

RESULTS

Two hundred thirty-three patients were included in the study. The mean annual number of patient days was 1742±322 days. Annual mean infection numbers, rates, and densities are shown in Table 1. Bloodstream infections were the most frequently detected HAI, followed by VAP.

The most frequently identified agent in the study was *Enterobacteriaceae* family, and infection numbers decreased over time (Table 2). Other agents identified were *Acinetobacter* spp. and *Pseudomonas aeruginosa*. Carbapenem resistance was determined in 50% of these pathogens . The highest handwashing rates during the study period were identified in nurses, followed by patient carers, and then by doctors (Table 3).

Table 1. Infection numbers, rates, and densities

	Infection number	Infection rate	Infection density
Bloodstream infection	4.6±2.3	2.1±1.4	2.6±1.1
Ventilator-associated pneumonia	2.5±1.8	1.2±1.0	1.3±0.9
Surgical site infection	0.67±0.81	0.30±0.33	0.37±0.44
Urinary tract infection	1.0±1.2	0.5±0.7	0.5±0.7
Meningitis	0.1±0.4	0.1±0.2	0.2±0.08
Total	9.0±3.9	4.2±2.8	5.0±1.5

Data are expressed as mean±standard deviation

Table 2. Infectious agents in the study and resistance rates, n (%)

	2015	2016	2017	2018	2019	2020	Total
Acinetobacter spp.	3	0	0	3	0	0	6
Carbapenem-resistant strain	1 (33%)			2 (66%)			3 (50%)
Pseudomonas aeruginosa	0	2	2	1	0	1	6
Carbapenem-resistant strain		2 (100%)	0 (0%)	0 (0%)		1 (100%)	3 (50%)
Enterobacteriaceae	10	3	7	3	2	1	26
ESBL-producing strain	1 (10%)	1 (33%)	3 (43%)	3 (100%)	1 (50%)	0 (0%)	9 (34%)
Staphylococcus aureus	2	0	1	1	0	0	4
MRSA	1 (50%)		0 (0%)	1 (100%)			2 (50%)

ESBL; extended spectrum beta lactamases

Table 3. Health personnel handwashing percentages

Doctors	31.8±12.5
Nurse	48.1±14.3
Cleaning personnel	30.9±26.2
Patient caregivers	33.9±28.2
GENERAL	42.4±15.8

Data expressed as mean±standard deviation

Table 4. Correlations between infection parameters

	Total infection number	Total infection rate	Total infection density	Patient days
Bloodstream infection rate	p=0.03 r=0.85	p=0.03 r=0.84	p=0.02 r=0.87	-
Ventilator-associated *pneumonia* numbers	p=0.03 r=0.83	p=0.04 r=0.82	-	p=0.05 r=0.80

Correlations between infection parameters are shown in Table 4. A strong correlation was determined between BSI rate and total number of infections (p=0.03, r=0.85), infection rate (p=0.03, r=0.84) and infection density (p=0.02, r=0.87). VAP was strongly correlated with total number of infections (p=0.03, r=0.83), total infection rate (p=0.04, r=0.82), and patient days (p=0.05, r=0.80). No correlation was determined between handwashing rates and infection numbers, rates, or densities.

DISCUSSION

The frequency of hospital infections, their distributions, and factors affecting increases or decreases in their incidence rates are determined through surveillance studies conducted by infection control committees. Problems are identified based on the data obtained, and the appropriate activity for identifying a solution is then carried out.[6] In the present study, the rate of HAI was 4.2%±2.8 and the density was 5.0±1.5. Previous studies from Turkey have reported various infection rates and densities. In Istanbul University Faculty of Medicine between 1 January and 30 June, 2010, reported infection rates and densities were 9.6% and 10.88%, while Adana Numune Education and Research Hospital between 1 January, 2012, and 31 December, 2016 the corresponding rates were 2.36% and 2.89%, respectively.[3,7]. The lower rates in the present study relative to the study from Istanbul suggested the involvement of various factors. Indeed, the neonatal and pediatric wards were being included in the study, bone marrow transplantation is not performed on pediatric patients in our hospital, diagnosis is not difficult to make through viral infection tests being performed when necessary, and rapid transfer of inpatients to the ward is realized once the indication for intensive care has disappeared. The higher rates obtained in our study than those from Adana may be associated with low compliance with hygiene among physicians, insufficient maximum barrier precautions being taken during catheter placement, catheters remaining in place for long periods, and a possession of sufficient data for diagnosis of nosocomial infections following active surveillance.

Consistent with other studies in the literature, the most common nosocomial infections in this study were BSIs and VAP.[8,9] In contrast to other, previous studies, the most frequent infectious agent in the PICU in the present study was the *Enterobacteriaceae* group, while *Candida* spp. reported in other studies were not among the first three.[7,8,10-12] Carbapenem resistance seen in *Acinetobacter* spp. and *Pseudomonas aeruginosa* strains was lower than relevant data reported by Kayseri Education and Research Hospital and Adana Numune Education and Research Hospital.[7,12] This is very likely related to a lower frequency of antibiotic use and to narrower spectrum antibiotics being employed.

Consistent with some previous studies, hand hygiene compliance rates in the present study were higher among nurses than among doctors.[13,14] However, Karahan et al.[15] reported no difference in compliance among the occupational groups. The higher hand hygiene compliance among nurses compared to doctors and other health personnel in the present research was attributed to their comparatively greater involvement in patient care, greater observation of the measures adopted by them, and to their being warned in the event of incorrect practices. Karaoğlu et al.[16] cited the difficulties inherent in being a doctor and male gender as risk factors for low compliance in physicians. In the present study, we thought that the low compliance rate might have derived from doctors feeling themselves to be clean, to their thinking that hand hygiene is more important in surgical procedures,

and to an absence of large numbers of role models among their own colleagues. Examination of the general literature shows that hand hygiene is correlated with infection rates.[4] However, no correlation was determined in the present study between handwashing rates, rates, and densities of infection, and the number of infections.

Prolonged stay in the ICU, mechanical ventilation exceeding 48 hours, intubation, immunosuppression, genetic diseases, underlying respiratory diseases, a history of broad-spectrum antibiotic use, and enteral nutrition have been cited as risk factors for the development of VAP.[17,18] A strong correlation was similarly observed in the present study between VAP and duration of hospitalization. We think that shortening lengths of hospital stay may be the most important factor in reducing VAP rates in the future. Although this study produced significant findings making a significant contribution to the existing literature, it also has a number of limitations. Our hospital's pediatric infectious diseases specialist only commenced work in 2018, for which reason, although the same guidelines were employed, various difficulties and deficiencies were experienced in terms of diagnosing HAI in the earlier period. Although catheter-associated infections have recently been described separately, BSI numbers, rates, and densities in the present study included both catheter-related and -unrelated cases which were evaluated in combination. Finally, although each HAI has its own variable specific risk factors, due to deficiencies in retrospective data, these parameters could not be assessed individually. Nonetheless, this study is the first on the subject from the relevant department of our hospital, and will be a useful guide for future more extensive and multi-perspective studies.

In conclusion, the annual total infection numbers, infection rates, and infection densities in the present study were similar to those in previous studies obtained from other centers. BSIs were the most common HAI. The most frequently identified HAI agent was the *Enterobacteriaceae* family. Other frequently identified agents, *Acinetobacter* spp. and *Pseudomonas aeruginosa*, exhibited carbapenem resistance rates of 50%. The highest rates of handwashing throughout the study period were observed among nurses, followed by patient carers, and then doctors. A strong correlation was determined between VAP and patient days.

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Children of Africa as Silent Victims of COVID-19 Pandemics

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In December 2019, there has been an increase in the cases of pneumonia in China especially in Wuhan spread to China and all over the World. On January 30th the WHO declared the situation of the outbreak as a public health emergency of international concern. In February, Africa registered the first case of COVID-19 and later in the second week of March, the WHO declared a pandemic. COVID-19 was expected to provoke more deaths in Africa than in other parts of the World but as seen now, the infection itself did not cause enormous loss of life according to the daily published number of cases. The effect of restrictions and other measures of mitigation taken by different governments of African countries to prevent the spreading of the disease need to be taken into consideration.[1-3]

The socioeconomic impact of these measures brought a bigger problem since Africa has already had its economic problem. Many people lost their jobs because of closed companies, because of those that stopped due to the lack of circulation of people and goods, closure of schools and other important places. Productivity reduced and lack of first need products was a problem in some countries. The fact that there is a percentage of people who work daily to live and also the number of displaced people as well as those who even though are not displaced but in limits of starvation makes it a bigger challenge.[4,5]

The closure of schools did not help many countries since they did not have a background in distance learning as well as are not technologically ready for online education. During these 9 months since the first case was reported in Africa, education has not been on the priority list for most African Governments.

Educational infrastructure and well trained human resources were the main challenges of African countries even before pandemics, it is almost impossible to fulfill physical distancing rules at

schools in general, especially primary school with more challenges. Since the lack of technological resources to support online lessons, lack of electricity in rural areas, and limited internet connection are still problems to solve.[6]

As a result, these factors have affected children in the following ways:[7-13]

1. Lack of good nutrition that was a problem even before the pandemic and during the pandemic, there is a lack of first need products and problems of food access;
2. Education and teaching should have been a continuous process, should continue even at home but the level of literacy is still a challenge to defeat and the children whose parents do not know how to read will not have access to information, this is what kills the society;
3. The closure of schools makes children more vulnerable to many forms of violence because it is more difficult to monitor pupils that are not in school. Others due to the economic impact of the pandemic may be forced to prostitution especially females and other forms of violence against children;
4. Information about COVID-19 prevention as well as ways of transmission seems not to reach every part and every child of Africa, in contrast, European countries were able to make information reach everywhere by using social media and local broadcast means, in some countries of Africa there are still limitations in this matter; so increasing awareness should be door by door to be effective and could be more terrible if not done correctly;
5. The number of laboratories and daily test capacity, as well as limitation in the number of laboratories, led to the low number of positive cases, though in some studies African countries having a high percentage of youth population contributed to less mortality and the existence of more asymptomatic patients;
6. Think about online lessons in places where less than 20% of the population have access to computers; and most of them are university students;
7. Lack of measures reflected from local problems during this pandemic, we have more children at home and it is boring when they are not able to share the same environment with their friends because of pandemics and do not have another way to overcome the loneliness;
8. The information about how to prevent the disease of COVID-19 is not accessible for children who cannot read, for those who have a visual deficiency, for those who have an auditive deficiency as well as some families with a low level of literacy. And the more interesting is that in some places people do not even believe that COVID-19 exists and some people think that they can defeat the disease with superstitious power and traditional plants;
9. Negative impact on the mental health of the parents due to loss of jobs and the difficulty in surviving led to social agitation which has a very negative impact on the relationship with their children;
10. Displaced families due to crises other than COVID-19 are more susceptible to other problems that could lead them to death;
11. Studies have shown that the more people are staying together and as predictable there is an increase in the incidence of violence mainly domestic violence;

Lack of short-time production leads to insecurity and lack of first need products. Since the pandemic diminishes the circulation, export-import most African countries are industrially weak and depend on the imported product of first need. Even before COVID-19, the number of people that are on break of starvation was 1.350.000.000 people according to WFP Mali, Burkina Faso, and Niger similar to other countries, this number is now 270.000.000 and by the end of this year, it is estimated to be millions of people have been displaced because of internal wars, civil wars, and coups.[14]

Lockdown in Africa makes fewer people die from COVID 19 but more people from the consequences such as food insecurity, lack of Access, the rise in prices of food, economic deterioration as well as a good number of people who lost their job because

of COVID-19. In this situation as we know Africa is a burden of infectious diseases. Malnutrition is going to increase and the susceptibility of dying from diseases that could otherwise be easily treated. Before the pandemic African children were very vulnerable to diseases especially infectious diseases, apart from the challenges mentioned above, we can conclude that there is an aggravation of the problem and the pandemic of COVID-19 makes it worse and worse.[14]

The budget of countries to respond to the challenges was insufficient even in periods before the pandemic. Therefore, African governments should do their best to prioritize the best interest of their children in the next year general budget plan so that they can continue their process of learning and have good health (physical, mental and social); reduce the differences between children of rural and urban areas and ensure that children are well protected against violence of every nature under the measures of restrictions that the pandemic can bring to us in the future; prepare a system that will be suitable with future decisions if the number of cases increases. As data suggests COVID-19 itself only causes hospitalization in a minority of the infected children, this appears that in the pandemics children are not a priority in many countries of Africa. Any plan or measure of mitigation to fight COVID-19 should put into consideration the major interest of children's rights because they are the most affected in every aspect of pandemics other than severe disease.

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