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Aims and Scope

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

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

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

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Acknowledgements: Any technical or financial support or editorial contributions (statistical analysis, English evaluation) towards the study should appear at the end of the article.

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Editorial

Dear JPR Readers,

We are proud and happy to announce that the third issue of "The Journal of Pediatric Research" in 2022 has been published.

The Journal of Pediatric Research is indexed in the Web of Science-Emerging Sources Citation Index (ESCI), Embase, the Directory of Open Access Journals (DOAJ), EBSCO, the British Library, CINAHL Complete Database, ProQuest, Gale/Cengage Learning, Index Copernicus, the Tübitak/Ulakbim TR Index, TurkMedline, J-GATE, IdealOnline, ROOT INDEXING, Hinari, GOALI, ARDI, OARE, AGORA, EuroPub, and the Türkiye Citation Index.

In this issue, we present to you 16 articles, including 13 original research studies and 3 case reports. In one article, the authors aimed to compare glucose, insulin, leptin, ghrelin, adiponectin, cholesterol, and triglyceride levels in the cord blood of newborn babies with and without fetal malnutrition. They found high adiponectin levels in the cord blood of those babies with fetal malnutrition. In this issue, you will have the opportunity to update your knowledge about allergic rhinitis and to read about its relationship with MPV. Another article describes different allergens in children and their frequency.

In this issue, there is a study which aims to compare the effects of breastfeeding and kangaroo mother care on pain levels and physiological changes associated with the hepatitis B vaccine injection in neonates. Readers will have the opportunity to read a study evaluating the impact of nurse support on chronic disease management in the pediatric intensive care unit. Additionally, there is an article evaluating the relationship between high immunoglobulin levels with respiratory functions and chronic infections in Cystic Fibrosis.

We thank the authors, referees, editorial team, and Galenos Publishing House for their support in the preparation of this issue.

We look forward to your contributions to our future issues.

Best wishes

İpek Kaplan Bulut

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Original Article

Does Fetal Malnutrition Affect Ghrelin, Leptin, Adiponectin and Insulin Levels in the Cord Blood of Newborns?

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ABSTRACT

Aim: Fetal malnutrition is a condition characterized clinically by the inability of subcutaneous adipose tissue and muscle mass to reach the normal amount or by significant intrauterine loss. The major hormones regulating fetal growth, fetal energy metabolism and adipogenesis are insulin, leptin, ghrelin and adiponectin. Cholesterol and triglycerides are very important in fetal growth in the last period of pregnancy. In this study, it was aimed to compare the glucose, insulin, leptin, ghrelin, adiponectin, cholesterol and triglyceride levels in the cord blood of newborn babies with and without fetal malnutrition.

Materials and Methods: Term babies born in our hospital were included in this study. Babies with a Clinical Assessment of Nutritional Status of 24 or below were considered as cases with fetal malnutrition, and those over 24 were considered as cases without fetal malnutrition. Glucose, insulin, leptin, ghrelin, adiponectin, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, very-low-density lipoprotein cholesterol and triglyceride levels were studied from blood samples taken from the umbilical cord after delivery.

Results: A total of 80 term newborn babies (40 babies with fetal malnutrition and 40 babies without fetal malnutrition) were included in this study. Birth weight, glucose and insulin values were found to be significantly lower in the group with fetal malnutrition ($p<0.001$; $p<0.001$; $p=0.047$, respectively), and adiponectin levels were found to be significantly higher ($p<0.001$).

Conclusion: In our study, adiponectin levels in cord blood were found to be high in infants with fetal malnutrition. Considering the anti-inflammatory role of adiponectin, high adiponectin levels in infants with fetal malnutrition may directly or indirectly reflect a protective mechanism.

Keywords: Fetal malnutrition, ghrelin, leptin, adiponectin, insulin

Introduction

Fetal malnutrition (FM) is characterized by the inability to attain optimal amounts of subcutaneous adipose tissue and muscle mass in fetus or by a significant intrauterine loss of them. FM along with its typical clinical features was first described by Scott and Usher (1) in 1964. The Clinical Assessment of Nutritional Status (CANSCORE) has been developed as a simple and quick method to identify FM. It can be used independently of current assessments based on population norms in term newborn infants (2). FM can occur at any birth weight. FM is the most common cause of intrauterine growth restriction (IUGR) (3).

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Fetal growth is a complex process regulated by genetics, maternal factors, the intrauterine environment, and maternal and fetal hormones. Insulin is one of the most important hormones involved in fetal growth. The main axis in regulation of fetal growth is glucose-insulin-insulin-like growth factor-1 (4). In many studies, the cord insulin level of infants with fetal growth restriction was significantly lower compared to those without fetal growth restriction (5,6).

Other hormones, such as leptin, ghrelin, and adiponectin, are the hormones involved in the growth and the regulation of energy, homeostasis and appetite during the fetal and early postnatal period. Plasma leptin concentrations reflect the overall amount of adipose tissue and are positively correlated with insulin resistance (7). Ghrelin increases body weight, secretion of growth hormone, creates a positive energy balance, diminishes energy expenditure and enhances lipid accumulation (8). Adiponectin modulates insulin action and has anti-atherogenic and anti-inflammatory effects. Adiponectin levels are inversely proportional to body fat content and negatively correlated with insulin resistance (9,10).

Apart from these hormones responsible for the growth of fetal adipose tissue, cholesterol and triglyceride with an indirect effect are also very important in the fetal growth. Although the pathogenesis of intrauterine growth retardation has not been elucidated precisely, it is known that metabolic changes in the mother contribute to this process. Cholesterol and triglycerides are also crucial in the growth of the fetus, especially during the third trimester of pregnancy (11). In this study, it was aimed to compare the glucose, insulin, leptin, ghrelin, adiponectin, cholesterol and triglyceride levels in cord blood of newborn infants with and without FM.

Materials and Methods

Patients

This study was approved by the Medical School Ethics Review Board (26.12.2018-20.478.486) and funded by the University Scientific Research Projects Office (Reference number: 2019-008). Term newborn infants (gestational age ≥38 weeks according to the last menstrual period) who were born alive in our hospital between May 2019 and October 2019 were included in this study. Multiple pregnancies, premature newborns (gestational age <38 weeks), stillbirths, mothers with pre-pregnancy diabetes, gestational diabetes, hypertension and those infants of mothers with premature rupture of membranes were excluded from this study. Informed consent was obtained from all patients included in this study. Between May 2019 and October 2019, 370 newborn babies were born term in our hospital. A total of 80 term newborn infants were included in this study. The newborn infants were examined, and their weight, height and head circumference measurements were made following delivery.

CANSCORE scoring method

The CANSCORE was calculated using the CANSCORE method (2) by the same pediatrician within the first 12-24 hours after delivery. Nine signs and symptoms are evaluated in the CANSCORE method (2). Scoring is performed by examining the infant's hair, cheek fullness, chin fat folds, subcutaneous fat tissue in the arms and legs, whether the skin is loose and easily grasped and pulled away, the appearance of the ribs and intercostal space, the skin and adipose tissue on the back, subcutaneous fat tissue in the abdomen, and the number and depth of skin folds in the gluteal region. In the CANSCORE method, a minimum of 1 (poor, severe FM) and a maximum of 4 (good, no malnutrition) points are given for each parameter. At the end of the evaluation, a minimum of 9 and a maximum of 36 points can be obtained. The cut-off value of the CANSCORE is 24.

Newborns with a CANSCORE of 24 or below are considered as cases with FM. Those with a CANSCORE greater than 24 are considered as those without FM. With regard to the weight percentile of the newborn infants, those with a birth weight below the 10th percentile were considered as SGA babies, those with a birth weight between the 10th and 90th percentiles as AGA babies, and those with a birth weight above the 90th percentile were considered as LGA babies. Ponderal index values were calculated by using the weight and height measurements of the newborns with SGA. Those with a Ponderal index of 2.25 or below were considered as asymmetrical SGA.

Blood samples

After the umbilical cord was clamped following delivery, blood samples were taken from the umbilical cord. Glucose, insulin, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HLD) cholesterol, very-low-density lipoprotein (VLDL) cholesterol, and triglyceride values were measured immediately. HOMA was calculated according to the formula: insulin (microU/L) x glucose (nmol/L)/22.5.

Another blood sample was centrifuged at 5,000 rpm for 10 minutes and the separated serum sample was stored

at -80 °C until leptin, adiponectin, and ghrelin levels were measured. After collecting all the blood samples, the ghrelin, leptin and adiponectin levels of the separated serum samples were measured using ELISA kits.

Statistical Analysis

Statistical analysis was performed using the "SPSS (Statistical Package for Social Sciences) 16.0 for Windows" program. T-test, chi-square test, One-Way ANOVA and Cohen's kappa coefficient methods were used to evaluate the data. A p-value less than 0.05 was considered as statistical significance.

Results

Eighty newborn infants, 40 with FM and 40 without FM, were included in this study. When the demographic characteristics of the infants were analyzed, the mean gestational age was 38.20±0.97 (38-41) weeks. Thirty-five (43.7%) of the infants were female and 45 (56.3%) were male. Mean birth weight was 3,316.18±445.75 gr (2,230-4,530), mean birth height was 47.66±1.65 cm (43-52), and mean head circumference was 34.70±1.67 cm (31-38.5). When the demographic characteristics of the 40 infants with and the 40 infants without FM were examined, statistically significant differences were found between their birth weight, birth head circumference, Ponderal index value, CANSCORE and birth weight according to gestational week (Table I).

With regard to the antenatal history of the FM and non-FM groups, it was noted that maternal age was similar in both groups. There were no statistically significant differences between the mothers' pre-pregnancy weight, post-pregnancy weight, height or body mass index. No significant differences were found between the education levels of the mothers, the age of the father, or the income levels of the family (Table II).

When the FM group and the non-FM group were compared, the glucose level in the cord blood of newborn infants was significantly lower in the FM group (p<0.001), and the insulin value was significantly lower in the FM group (p=0.047). There was no significant difference between the groups with regard to leptin and ghrelin levels. The adiponectin level was significantly lower (p<0.001) in the FM group. When the lipid profile of the cord blood of the newborns in the FM and non-FM groups was

Table I. Demographic characteristics of the groups with and without fetal malnutrition

	Fetal malnutrition (+) (n=40)	**Fetal malnutrition (-) (n=40)**	**p-value**
Sex (n, %) - Female - Male	 15 (37.5) 25 (62.5)	 20 (50) 20 (50)	0.184
Birth weight (mean ± SD) (gr)	3.127.62±368.14	3.504.75±440.48	**<0.001**
Birth height (mean ± SD) (cm)	47.45±1.84	47.87±1.41	0.252
Head circumference (mean ± SD) (cm)	34.26±1.64	35.13±1.60	**0.018**
Ponderal index (mean ± SD) [(g/cm^3) x 100]	2.92±0.30	3.18±0.37	**0.001**
Birth method (n, %) - SVD - C/S	 2 (5) 38 (95)	 1 (2.5) 39 (97.5)	0.500
Gestational age (mean ± SD) (week)	38.01±1.12	38.42±0.74	0.058
Gestational age according to ultrasound (mean ± SD) (week)	37.72±1.32	38.17±1.03	0.094
Intrauterine growth restriction (n, %)	4 (10)	3 (7.5%)	0.500
CANSCORE (mean ± SD)	21.20±5.52	29.70±3.79	**<0.001**
APGAR score (median, min.-max.) - 1st minute - 5th minute	 8 (6-9) 9 (8-10)	 8 (7-9) 9 (8-10)	 0.728 1.000
Birth weight according to gestational week (n, %) - SGA - AGA - LGA	 1 (2.5) 39 (97.5) 0 (0)	 0 (0) 33 (82.5) 7 (17.5)	**0.014**

SD: Standard deviation, min.: Minimum, max.: Maximum, CANSCORE: The Clinical Assessment of Nutritional Status, SVD: Spontaneous vaginal delivery, C/S: Caesarean section, SGA: Small for gestational age, AGA: Appropriate for gestational age, LGA: Large for gestational age

compared, no significant differences were found in terms of total cholesterol, LDL cholesterol, HDL cholesterol, VLDL cholesterol, or triglyceride levels (Table III).

Discussion

Even though it is generally accepted that fetal growth restriction poses an increased risk for perinatal morbidity and mortality, the definition of fetal growth restriction is still problematic. In order to identify FM, a simple and quick method has been developed which can be used independently of the current assessments made according to population norms in term newborns. This method is called CANSCORE. FM can occur at any birth weight.

The weight, height and head circumference of a newborn with FM may or may not be within normal limits (2). The cut-off value for the CANSCORE is 24. Infants with a CANSCORE of 24 or below are considered as cases with FM. In a study conducted by Metcoff (2), the prevalence of FM via the CANSCORE method was found to be 10.9%. In

Table II. Antenatal characteristics of the groups with and without fetal malnutrition

	Fetal malnutrition (+) (n=40)	**Fetal malnutrition (-) (n=40)**	**p-value**
Mother's age (mean ± SD)	30.75±5.15	30.00±4.51	0.491
Mother's pre-pregnancy weight (mean ± SD) (kg)	72.43±16.42	72.25±16.77	0.960
Mother's weight at the end of pregnancy (mean ± SD) (kg)	84.71±15.39	82.65±16.43	0.564
Mother's weight gain during pregnancy (mean ± SD) (kg)	12.27±4.85	10.42±5.30	0.108
Mother's height (mean ± SD) (cm)	162.65±5.82	160.42±6.21	0.102
Mother's body mass index (mean ± SD) (kg/cm^2)	27.35±6.13	28.07±6.81	0.621
Body mass index (n, %) - Below normal - Normal - Overweight - Obese	 1 (2.5) 18 (45) 9 (22.5) 12 (30)	 0 (0) 15 (37.5) 14 (35) 11 (27.5)	0.493
Mother's illiteracy (n, %)	5 (12.5)	3 (7.5)	0.506
Paternal age (mean ± SD)	33.65±5.27	33.87±4.71	0.841
Family income rate (mean ± SD) (Turkish Liras)	2.877.50±1.777.27	2.458.00±1.133.18	0.212

SD: Standard deviation

Table III. Mean glucose, insulin, HOMA, leptin, ghrelin, adiponectin and lipid profile values in cord blood of infants with and without fetal malnutrition

	Fetal malnutrition (+) (n=40) (Mean ± SD)	**Fetal malnutrition (-) (n=40) (Mean ± SD)**	**p-value**
Glucose (mg/dL)	51.20±13.02	66.70±19.58	**<0.001**
Insulin (mIU/mL)	5.44±3.80	10.28±14.65	**0.047**
HOMA	0.70±0.52	2.21±4.78	0.051
Leptin (ng/mL)	5.05±4.46	6.79±7.23	0.201
Ghrelin (ng/mL)	0.42±0.78	0.37±0.11	0.723
Adiponectin (ng/mL)	3.74±0.48	3.32±0.49	**<0.001**
Cholesterol (mg/dL)	66.60±22.23	64.92±21.28	0.732
LDL cholesterol (mg/dL)	29.30±16.73	28.77±18.09	0.893
HDL cholesterol (mg/dL)	31.10±8.86	30.30±7.52	0.665
VLDL cholesterol (mg/dL)	6.20±6.28	5.85±4.06	0.768
Triglyceride (mg/dL)	31.22±31.04	29.35±20.14	0.750

SD: Standard deviation, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, VLDL: Very-low-density lipoprotein

a study conducted in our hospital in 2011, the frequency of FM in term newborns via the CANSCORE method was found to be 9.9% (12). In our study, the mean CANSCORE of the newborns with FM was 21.20±2.52 (16-24), and the mean CANSCORE of the newborns without FM was 29.70±3.79 (25-36). The CANSCORE was significantly higher in the group without FM ($p<0.001$). There was a statistically significant difference in birth weights according to the gestational age of the newborns in the groups with and without FM ($p=0.014$). Birth weight and birth head circumference were significantly lower in the group with FM than in the group without FM ($p<0.001$, $p=0.018$). There was no significant difference between average lengths at birth ($p=0.252$). The Ponderal index was significantly higher in the group without FM ($p=0.001$).

Fetal adipose tissue maturation in intrauterine life begins in the second trimester of pregnancy and further enhances during the third trimester. Fetal adipose tissue is necessary for lipid and more importantly, glucose metabolisms, as deficiency of adipose tissue leads to malnutrition and its excess results in obesity (13).

Adipokines are peptides produced mainly by adipose tissue. They play a critical role in energy homeostasis and metabolic regulation, and play a role in intrauterine growth (14). Fetal growth restriction hinders the proper formation of fat tissue in the fetus and can impair metabolic functions and endocrine secretions related to adipose tissue. In a rat model of FM, postnatal leptin administration reduced metabolic abnormalities in newborn rats (15). It has been reported that leptin levels in the cord blood are low in newborns with IUGR. These infants gain weight rapidly after birth and are prone to metabolic syndrome in adulthood (16,17). A positive correlation was found between fetal birth weight and fetal serum leptin levels. Leptin levels are lower in SGA infants (18).

Regardless of gestational age, birth weight is positively correlated with leptin levels (19). A positive correlation was found between serum leptin and glucose in term infants. It has been shown that there is a positive correlation between leptin and insulin by anthropometric measurements (20). In our study, blood glucose and insulin levels were significantly lower in the FM group, and leptin levels were reduced, although not significantly ($p<0.001$, $p=0.047$, $p=0.201$). In our study, insulin and leptin levels in the cord blood of newborns with FM were lower compared to those without FM and this finding is consistent with the literature.

Another peptide hormone which is crucial in fetal growth and reduces body weight and food intake due to its action as a leptin antagonist is ghrelin. Ghrelin increases body weight, enhances the secretion of growth hormones, produces a positive energy balance, reduces energy expenditure and promotes lipid accumulation (8). Regardless of gestational age, birth weight and total ghrelin exhibit a negative correlation (19). In our study, ghrelin levels were found to be high, although this was not significant in the FM group ($p=0.723$).

Another adipocytokine involved in intrauterine growth is adiponectin. Adiponectin is an indicator of insulin sensitivity and fatty acid oxidation (21). Therefore, decreased adiponectin levels may accompany increased insulin levels in infants with IUGR. It is thought that fetal maturation, hence the increase in fetal weight, affects cord blood adiponectin levels (22,23). SGA infants have reduced adiponectin levels. In one study, adiponectin levels in the cord blood of infants with IUGR were significantly lower than in the control group (24). In our study, unlike the findings reported in the literature, the level of adiponectin in the cord blood was significantly higher in those infants with FM compared to those without FM. Considering the anti-inflammatory role of adiponectin and pro-inflammatory role of leptin, we thought that low leptin levels and high adiponectin levels may directly or indirectly reflect a protective mechanism against chronic stress caused by FM.

Fetal adipose tissue is also essential for lipid metabolism because its deficiency leads to malnutrition (13). As Dios Garcia Diaz et al. (25) stated, the correlation of the lipoprotein profile in cord blood with fetal development parameters reveal conflicting results. While the relationship between lipid concentrations in cord blood and anthropometric measurements were found to be significant in certain studies, it was not reported to be significant in other studies (25,26). There were no significant differences in total cholesterol, LDL, HDL, VLDL cholesterol and triglyceride levels in cord blood, especially in normal birth weight infants with IUGR compared to healthy infants (27,28). In our study, there was no significant difference in lipid levels between the groups with and without FM. This may be due to the fact that the birth weights of the majority of infants in the with FM and without FM groups were compatible with their week of birth.

Study Limitations

The low number of cases and lack of long-term outcomes for patients are the limitations of this study.

Conclusion

The evaluation of fetal growth by birth weight alone can be misleading. Adipokines, particularly leptin and adiponectin, play a regulatory role in fetal growth. Given the anti-inflammatory role of adiponectin, high adiponectin levels in infants with FM may directly or indirectly reflect a protective mechanism.

Ethics

Ethics Committee Approval: This study was approved by the Medical School Ethics Review Board (26.12.2018-20.478.486) and funded by the University Scientific Research Projects Office (reference number: 2019-008).

Informed Consent: Informed consent was obtained from all patients included in this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.T., B.E., F.T., E.Ö., Design: S.T., B.E., F.T., E.Ö., Data Collection and/or Processing: E.Ö., Analysis and/or Interpretation: B.E., F.T., Literature Search: S.T., B.E., F.T., E.Ö., Writing: S.T., B.E., F.T., E.Ö.

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

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Original Article

Utility of Procalcitonin in the Engraftment Phase of Hematopoietic Stem Cell Transplantation in Children

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ABSTRACT

Aim: In hematopoietic stem cell transplantation (HSCT), the phase of engraftment which can be described as an "immunogenic storm", is also vulnerable to infections and it has been always very hard to discriminate the cause of fever in this special period of HSCT. In this study, we aim to determine if procalcitonin (PCT) could be used to define the cause of fever in the engraftment phase of HSCT.

Materials and Methods: This study involves 81 patients who consecutively underwent allogeneic HSCT between October 2017-June 2020 in our pediatric HSCT unit. The patients were divided into two groups due to the origin of the fever during engraftment as infectious fever group (n=42) and the non-infectious fever group (n=39).

Results: The median duration of fever for all groups was 4 days (1-11 days) and it was significantly lower in the non-infectious fever group compared to the infectious fever group (3 vs. 4 respectively p=0.001). The median PCT levels was 0.6 ng/mL (0.04-83) for all groups and it was significantly higher in the infectious fever group compared to non-infectious (1.4 vs. 0.3 p<0.001). According to ROC analysis, the cut-off PCT level of 0.515 ng/mL or more had an AUC of 0.817 and may predict the infectious fever with a sensitivity of 81% and a specificity of 76.9%.

Conclusion: We observed that PCT may be used to discriminate infectious fever from non-infectious fever at the engraftment phase of HSCT and PCT could be a useful marker for antibiotic treatment strategy.

Keywords: Engraftment, hematopoetic stem cell transplantation, procalcitonin

Introduction

In hematopoietic stem cell transplantation (HSCT), the phase of engraftment can be described as an "immunogenic storm" and it is susceptible to infections because of severe neutropenia. Fever is the most commonly seen symptom associated with both these faces of engraftment. It has always been very hard to discriminate the cause of the fever in this special period of HSCT. This uncertainty between infectious or immunogenic fever is problematic due to an unnecessary use of antibiotics and delays in choosing the proper therapy.

Procalcitonin (PCT) is produced in C-cells of the thyroid gland and is a propeptide of levels are measured. However, the synthesis of PCT can increase as a result of an increase

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in endotoxins and/or cytokines. Increased PCT levels are detected in bacterial, parasitic, and fungal infections but PCT is not observed in healthy individuals, with only small increases seen in viral infections (1,2). Additionally, the diagnostic value of PCT is more discriminative than C-reactive protein (CRP) in differentiating infections from non-infectious processes accompanied by fever including for neutropenic patients (1,3). PCT has a long serum half-life of 25 to 30 hours and in the case of infections, PCT levels increase in 3 to 4 hours while CRP needs 24 to 48 hours to rise significantly (4,5). Apart from infections, CRP can be a more reliable marker for inflammatory processes, as it is well known that CRP significantly increases in engraftment syndrome (6).

In this study, we aimed to determine if PCT could be used to define the cause of fever in the engraftment phase of HSCT. Although inflammatory fever without infections can also cause PCT to increase, the level of this increase is not clear for the engraftment phase of HSCT. We measured the peak PCT level at the first fever episode in the engraftment phase and tried to define a cut-off value for PCT in order to discriminate infectious and non-infectious causes.

Materials and Methods

This retrospective study involved 81 pediatric patients who consecutively underwent allogeneic HSCT between October 2017 and June 2020 in our pediatric HSCT unit. This study was approved by the Medical Research Ethics Committee (13.10.2021-16/01).

Those patients who had at least one febrile episode in the engraftment phase (within 4 days of engraftment) were included. Those patients with no febrile episode or febrile episodes where PCT and CRP levels were not assessed were excluded. Additionally, febrile episodes before or after the engraftment phase were excluded from this study. Although this study only focused on fever at the engraftment phase, other clinical findings besides fever were evaluated and engraftment syndrome was defined as mentioned in the Spitzer Criteria (7).

The patients were divided into two groups according to the origin of their fever. The infectious fever group consisted of those patients who had infectious events as defined below and the non-infectious fever group was comprised of all the other patients who had no infectious events. We compared these two groups regarding the the day of the fever, the duration of the fever, and their PCT, and CRP levels.

Infectious Events

A single oral temperature of ≥38.3 C or ≥38 C sustained over one hour was defined as a fever (8). Positive blood culture was defined as bacteremia (two positive cultures were needed for coagulase-negative staphylococci). Urinary tract infection was considered when >100,000 colonies of bacteria/mL were observed in a urine culture. Cytomegalovirus (CMV) reactivation was defined as quantitative polymerase chain reaction (PCR) >1,000 copy (Anatolia Bosphore CMV Quantification Kit Istanbul, Turkey). Pulmonary infiltrates on chest X-ray/computerized tomography which could not be explained by any other reasons were defined as pneumonia. Any other localized inflammation except for pneumonia was defined as a local infection.

Supportive Care and Management of Febrile Episodes

Bone marrow transplantation was performed in HEPA filtered air-conditioned single rooms. All patients received fluconazole and acyclovir as prophylaxis from the initiation of conditioning, co-trimoxazole prophylaxis was initiated after engraftment. Broad-spectrum antibiotics were initiated in case of any febrile episodes and blood, urine cultures or clinical samples as indicated such as pus culture or swab were taken. Viral screening via PCR, influenza, and severe acute respiratory syndrome-coronavirus-2 were analyzed if necessary. Antibiotics consisting of an antipseudomonal β-lactam, a fourth-generation cephalosporin, or a carbapenem were preferred as the first-line therapy. This was revised later depending on microbiological information or clinical evolution. If the fever persisted for more than 96 hours, empirical broad-spectrum antifungal treatment was initiated.

PCT and CRP Measurements

For each episode of fever, we had a measurement of PCT and CRP within 24 hours from its onset. We continued PCT and CRP measurements as clinically indicated within the engraftment phase. Due to the variable duration of serial measurements, we only included the peak PCT and CRP levels within the engraftment phase. PCT was measured by PCT fast test kit immunofluorescence assay (Getein Biotech, Inc. Nanjing, China) and CRP by turbidimetry (Sentinel Milan, Italy). Normal values are <0.5 ng/mL for PCT and <5 mg/L for CRP. According to the manufacturer's recommendation, we kept in mind any interferents which might have influenced the test results.

Statistical Analysis

The Mann-Whitney U test was used to assess any differences between the two groups. The diagnostic relevance was estimated as sensitivity, specificity, and the positive and negative predictive values. Levels of sensitivity and specificity were plotted on the receiver operator characteristic (ROC) curve. The area under the curve (AUC), was calculated by trapezoid integration. While an area of 0.5 denotes no discrimination, an area of one denotes full discrimination. According to optimized sensitivity and specificity, the best cut-off value was chosen. Kaplan and Meier was used to analyze overall survival (OS). The Statistical Program for Social Science (IBM Corp. Released 2011, Version 20.0, Armonk, NY) was used in calculations.

Results

Patient Characteristics

The patient group consisted of 81 consecutive pediatric patients (55 males; 67%, 26 females; 33%) with a median age of 64 months (range 1-248 months) who underwent allogeneic HSCT for malign disease (n=26, 33%) or non-malign disease (n=55, 67%). The patients received stem cell transplants from a matched unrelated donor (n=45; 56%), a matched sibling donor (n=19; 23%), a matched family donor (n=10; 12%) or a haploidentical donor (n=7; 9%). Stem cell sources included bone marrow (n=33), peripheral blood (n=44), both bone marrow and cord blood (n=3) and both bone marrow and peripheral blood (n=1). The conditioning was myeloablative for 77 patients and only four patients had a non-myeloablative regimen. The patient characteristics are given in Table I.

Origin of Fever

The patients were divided into two groups according to the origin of their fever during engraftment. Those patients with infectious fever (n=42) had either bacteremia (n=30), CMV reactivation (n=10), bacteriuria (n=1) or pneumonia (n=1). According to their blood cultures, 17 patients had gram-positive bacteria, and 13 patients had gram-negative bacteria. There was no significant difference between the type of bacteria in terms of CRP levels, PCT levels, duration of fever, or the post-transplant day of fever.

Table I. Characteristics of patients according to their origin of fever

Patient characteristics	All (n=81)	Infectious fever (n=42)	Non-infectious fever (n=39)	p-value
Median age at transplant, months	64 (1-248)	56 (6-252)	80 (1-248)	0.057
Disease type				0.268
Malign	26 (33%)	11 (26%)	15 (38%)	
Non-Malign	55 (67%)	31 (74%)	24 (62%)	
Gender				0.320
Female	26 (33%)	12 (28%)	14 (36%)	
Male	55 (67%)	30 (72%)	25 (64%)	
Donor type				0.527
Matched unrelated	45 (56%)	22 (52%)	23 (59%)	
Matched sibling	19 (23%)	10 (24%)	9 (23%)	
Matched family	10 (12%)	6 (14%)	4 (10%)	
Haploidentical	7 (9%)	4 (10%)	3 (8%)	
Stem cell source				0.317
Peripheral blood	44 (54%)	19 (45%)	25 (64%)	
Bone marrow	33 (40%)	20 (47%)	13 (33%)	
Bone marrow + Cord blood	3 (4%)	2 (5%)	1 (3%)	
Bone marrow + Peripheral blood	1 (2%)	1 (3%)	-	
Conditioning regimen				0.926
Myeloablative	77 (95%)	40 (95%)	37 (95%)	
Non-myeloablative	4 (5%)	2 (5%)	2 (5%)	

The median day of post-transplant CMV reactivation was 13 (8-17) days. In the group with infectious fever, the duration of fever was significantly lower in those patients with CMV reactivation compared to those patients without reactivation (3 days vs. 5 days respectively, p=0.04). Regarding the duration of fever, those patients with or without CMV reactivation had similar findings regarding their post-transplant day of fever, PCT, and CRP levels (Table II).

All of the 39 patients in the non-infectious fever group had no positive blood/urine culture, no CMV reactivation, and no infiltration in the radiological work-up of the chest. Amongst these 39 patients, only 16 met the criteria for engraftment syndrome, while the rest only had fever which could not be explained by an infectious origin.

Comparison of the Infectious Fever Versus the Non-infectious Fever Groups

According to the transplant characteristics, there were no significant differences between the two groups regarding gender, age, type of disease, stem cell source, or donor type.

The median neutrophil engraftment time and post-transplant days of fever of the whole group were 11 days (8-18 days) and 9 days (4-21 days), respectively. There were no significant differences between the groups regarding neutrophil engraftment time or post-transplant days of fever.

The median duration of fever for all groups was 4 days (1-11 days) and it was significantly lower in the non-infectious fever group compared to the infectious fever group (3 vs. 4 respectively p=0.001). The median PCT level was 0.6 ng/mL (0.04-83) for all groups and it was significantly higher in the infectious fever group compared to non-infectious (1.4 vs. 0.3: p<0.001). The median CRP levels was 72 mg/dL (0.3-306) and it was significantly higher in the infectious group (85.5 vs. 60: p=0.026) (Table III).

According to ROC analysis, a cut-off PCT level of 0.515 ng/mL or more had an AUC of 0.817 and may predict infectious fever with a sensitivity of 81% and a specificity of 76.9% (Figure 1).

OS (3 years) for all the patient groups was 80.2% (±4.7). Regarding the cut-off PCT level (0.515 ng/mL), 3 year OS for those patients whose PCT level was <0.515 ng/mL was 82.0% (±7.0) and for those patients whose PCT level was ≥0.515 ng/mL was 78.1% (±6.5) (p=0.585).

Discussion

Our aim in this study was to show whether PCT could be used as a marker to differentiate between infectious and non-infectious fevers at the engraftment phase of HSCT. The engraftment phase of HSCT has two challenging characteristics to test a marker for such discrimination; (1) the last period of aplasia just before the neutrophil

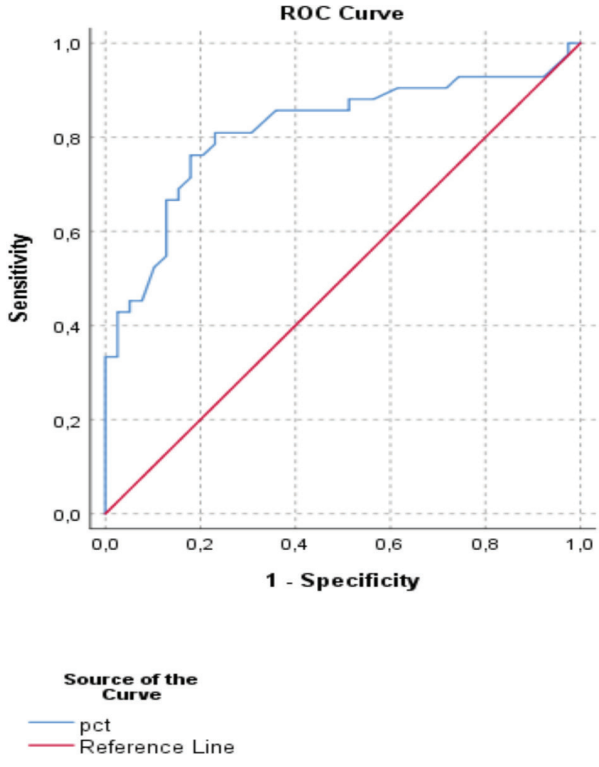

Figure 1. PCT level of 0.515 ng/mL or more had an AUC of 0.817 and may predict the infectious fever with a sensitivity of 81% and a specificity of 76.9%

PCT: Procalcitonin, AUC: Area under the curve

Table II. Comparison of the patients regarding CMV reactivation

	No CMV reactivation (n=31)	CMV reactivation (n=11)	p-value
PCT (ng/mL)	1.40 (0.05-83.00)	1.40 (0.17-11.30)	0.466
CRP (mg/L)	92.00 (4.90-306.00)	72.00 (17.00-192.00)	0.271
Post-HSCT day of fever	9.00 (3.00-21.00)	11.00 (7.00-14.00)	0.124
Duration of fever (day)	5.00 (1.00-11.00)	3.00 (1.00-8.00)	0.040

CMV: Cytomegalovirus, PCT: Procalcitonin, CRP: C-reactive protein, HSCT: Hematopoietic stem cell transplantation

Table III. Comparison of characteristics of infectious and non-infectious fever

	Infectious fever median (range)	Non-infectious fever median (range)	p-value
PCT (ng/mL)	1.40 (0.05-83.00)	0.30 (0.04-3.60)	<0.001
CRP (mg/L)	85.50 (4.90-306.00)	60.0 (0.30-236.00)	0.026
Post-HSCT day of fever	10.00 (3.00-21.00)	9.00 (4.00-19.00)	0.383
Duration of fever (day)	4.00 (1.00-11.00)	3.00 (1.00-8.00)	0.001

PCT: Procalcitonin, CRP: C-reactive protein, HSCT: Hematopoietic stem cell transplantation

increments and (2) high cytokine release just after the neutrophil increments.

The effectiveness of PCT in the follow-up of neutropenic patients is controversial in the literature. Although it has been shown that peripheral blood mononuclear cells are a major source of PCT, we detected high PCT levels in the neutropenic phase of HSCT. Our findings were also consistent with those studies in which PCT levels seemed to be independent of the cell count (9-11).

As previously reported, cytokine release was the main component of the engraftment phase so we may easily hypothesize that the cytokine release was the most probable etiology of inflammatory fever in our non-infectious group (12,13). Additionally, it may be acceptable to test PCT as a marker to differentiate between infections and inflammations which are caused by this cytokine release. In one of the early studies on the role of PCT in HSCT to discriminate infection from inflammation, it was found that PCT was non-effective (14). That study had two main limitations as it only involved 12 patients and it analyzed all inflammatory complications after HSCT rather than focusing on a certain complications or periods. In another study, PCT was defined as a biomarker for engraftment syndrome which could be accepted as an inflammatory process (13). Although it was known that even PCT could increase in cases of inflammation, these changes can be distinguished from infections with a cut-off value (15). In our study, we not only evaluated PCT changes in patients diagnosed with engraftment syndrome, but we also tried to show its discriminative value for infectious and non-infectious fever in the engraftment phase by defining a cut-off value.

CMV reactivation is closely followed up especially in the early phases of stem cell transplantation. It is not one of the prominent reasons for fever, but previously, CMV was solely associated with fever in stem cell transplantation (16). Although viral infections are known to be related to small/modest PCT increases, in our study, we included CMV reactivation in the infectious fever group (15). Additionally, we found that CMV reactivation had similar median PCT values to the other causes of infectious fever consistent with our study design.

In our study group, anti-thymocyte globulin (ATG) was used in conditioning before HSCT and it is well known that ATG impacts inflammatory markers such as CRP and PCT (17). As mentioned in previous studies, the impact of ATG is transient and it is expected that the inflammatory markers reach their baseline values after approximately 4 days (18). All the patients in this study had fever after the cut-off time of ATG so we can exclude the impact of ATG on this study.

Although we focused on the PCT for the discrimination between infectious and non-infectious fever at the engraftment phase, CRP levels were also significantly higher for the infectious fever group. This data was consistent with the findings of Hambach et al. (19) regarding the comparison of PCT and CRP in HSCT. Unlike well-accepted data, Hambach et al. (19) showed that for the detection of bacterial or fungal infections in HSCT, PCT did not have a superior diagnostic value to that of CRP. We could not explain the exact dynamics of these inflammatory markers in HSCT, but both of them may predict infectious disease at the engraftment phase, with PCT having a statistical superiority over CRP.

Study Limitations

There are some limitations for this study, namely; (1) this is a retrospective study (2) we have no serial measurements of PCT and CRP so we used the peak values in the fever episode and (3) although we assumed that cytokine release in the engraftment phase was the main reason for non-infectious fever, we had no cytokine measurements.

Conclusion

In this study, we observed that PCT and CRP may be used to discriminate infectious fever from non-infectious fever at the engraftment phase of HSCT. Within the engraftment phase, PCT levels <0.515 ng/mL for the first fever episode may predict non-infectious etiology with a sensitivity and specificity of 81% and 76.9%, respectively and PCT may

be a useful marker for antibiotic treatment strategy. CMV reactivation can also cause a modest change in PCT levels. Although these results are promising for the proper therapy of fever in this phase, our results should be confirmed in prospective studies with more patients.

Ethics

Ethics Committee Approval: This study was approved by the Medical Research Ethics Committee (13.10.2021-16/01).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Data Collection or Processing: K.Y., D.P., S.Ç., S.Z., Analysis or Interpretation: K.Y., G.K., V.U., V.H., A.Y., Writing: K.Y., V.U.

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

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Original Article

Determination of the Relationship Between Disease Managements and the Perception of Nursing Support of Parents Whose Children are Monitored in an Intensive Care Unit

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ABSTRACT

Aim: This study was conducted descriptively to determine the relationship between disease managements and the perception of the support given by nurse of the parents whose children were monitored in a Pediatric Intensive Care Unit (PICU).

Materials and Methods: This study was carried out between August-December 2018 in a PICU. The sample of the study comprised 108 parents whose children were being monitored for a chronic disease diagnosis. The study data were collected via two data collection forms, "The Family Management of Childhood Chronic Conditions" (FaMM) and "Nurse Parent Support Tool" (NPST).

Results: The parents' gender, knowledge about the disease and the FaMM three sub-dimension score averages were not statistically significant ($p>0.05$). However, the difference between the parents' educational background, income status, the factors of support from the social environment and the sub-dimension score averages were significant ($p<0.05$). While the difference between the interviewed parents' gender and income status and NPST score averages were not significant ($p>0.05$); the difference between the interviewed parents' educational background, knowledge about the disease, the status of support from the social environment and NPST score averages were significant ($p<0.05$).

Conclusion: It was concluded that as the perceived support from nurses of the parents of the child with chronic disease increases, the disease management increases.

Keywords: Pediatric intensive care, parents, nurse support, disease management

Introduction

Chronic diseases keep increasing rapidly and are already the most important health problem in the world, especially in industrialized countries. The number of children with chronic illnesses has increased significantly over the last two decades. Incidents of death due to chronic illnesses now rank higher than hunger, mother and child mortality, and infections (1). Chronic diseases are also among the most important health problems in Turkey. According to estimates, the incidence of chronic illnesses in children is between 10-15% in the population of under 18 years of age and it reaches 30-40% with the inclusion of children with mental, sensory, learning, and behavioral problems (2-4).

Chronic diseases for children pose serious challenges from a health management perspective (5). Most of the children with chronic illness are cared for at home and their

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primary caregivers are their parents. Therefore, healthcare workers should remember that the experience of illness affects all family members, not only the patient. Parents often play an important role in the care of childhood chronic diseases (6). Nurses who are in close contact with children and their families are indispensable members of the healthcare team as primary caregivers. Therefore, they increasingly assume leadership roles especially in the management of chronic illnesses (7,8). Pediatric chronic diseases have three levels of consequences; 1) those experienced by the child or individual family members (school absence, activity limitation, psychosocial and behavioral problems) and 2) those experienced by the family system (disruption of usual routines, alteration of roles and relationships) and 3) other outcomes related to the family's interactions with the child's health care providers. When the literature is examined, it is seen that nurse given support plays an important role in the management of the disease for the child and family (9-11). In line with this, the ability to cope with stress, acceptance of the illness, and thus adaptation of the child to the illness are all significantly associated with nursing support.

Although chronic disease management and nurse support are an important issues for childhood diseases, no study has been carried out in this area in the pediatric intensive care unit (PICU) to the best of our knowledge. This study was carried out to determine the relationship between the perceived support given by nurses and disease management of the parents whose children were followed up in the PICU with a diagnosis of chronic illness.

Materials and Methods

Sample and Procedures

This study was conducted descriptively between August and December 2018 at the PICU of the University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital, in İstanbul, Turkey.

The study universe consisted of the parents of 150 children who had been followed up in the unit within the previous year (2017) with a diagnosis of a chronic illness. The sample of the study was based on the formula with a known number of individuals in the universe. The sample consisted of 108 parents who did not have any health problems to prevent communication and who agreed to participate in this study. Data were collected 24 hours after the child was admitted to the PICU. The parents filled out the forms themselves in a quiet place where they were alone.

Instruments

Data were collected using The Data Collection Form, The Family Management of Childhood Chronic Conditions (FaMM) and the Nurse Parent Support Tool (NPST), all of which investigated the characteristics of children and their parents.

The data collection Form: This form consists of questions including socio-demographic characteristics regarding the parents and their children, information on the disease, and the effect of the disease on the parents. In order to test the comprehensibility of the data collection forms, a pilot study was conducted with 5 parents.

FaMM: It was developed by Knafl et al. (10). The original scale consists of 53 items and six sub-dimensions. The Turkish validity and reliability study was conducted by Ergun et al. (12). The Turkish version of the scale consists of 42 items and three sub-dimensions. The first dimension is "illness management and the daily life of the child" and higher scores indicate a rather normal life and families finding themselves more capable of illness management. The second dimension is the "difficulties of life and the impact of illness" and the higher the score, the more severe the condition is and the more the difficulties are experienced. The third dimension is "parental agreement" and high scores indicate that parents work together in the management of the child's illness. Each item in the scale is scored from 1 to 5 (10,12). The Cronbach's alpha coefficients of the 3 sub-dimensions of the FaMM in parents in the sample group were 0.93, 0.87, 0.84 respectively.

NPST: This was developed by Miles et al. (13) to measure the level of support provided to parents by the nurses. It was adapted to Turkish and validated by Yiğit et al. (8). The scale consists of four sub-dimensions: "information and communication support, emotional support, respect support, and quality healthcare". It has 21 items in a 5-point Likert type scoring system. The scale is scored by adding the scores of the items answered and dividing them by the total number of items and possible scores range from 1 to 5. High scores reflect increased support which parents receive from nurses (8). The Cronbach's alpha coefficients of the 4 sub-dimensions of the NPST for the parents in the sample group were 0.76, 0.68, 0.68, 0.67 respectively.

Statistical Analysis

The data obtained in this study were analyzed using the SPSS for Windows 22.0 program. In the data assessment, the number, percentage, mean, and standard deviation among descriptive statistical methods were used.

Independent t-test and ANOVA tests were used for data analysis. Regression analysis was performed to determine the relationship between continuous variables. The results were evaluated at a 95% confidence interval and $p<0.05$ was the significance level.

Ethical Approval

This study was approved by the Okan University Ethics Committee (approval number: 96, date: 04.07.2018). The parents were informed about the research and their written consent was obtained.

Results

More than half (61.1%) of the children participating in this study were girls. 27.8% of the children were in the 7-12 years age range. Of the parents who participated in this study and provided care for their children, 81.5% were mothers and 30.6% had a university degree. It was found that 51.8% of the parents' income equaled their expenses. Among the parents, 57.4% stated that they were adequately informed about the illness and 54.5% stated that they did not receive support from their social circle (Table I).

The difference between the gender and age of the children whose parents participated in this study and the mean sub-dimension FaMM scores was statistically insignificant ($p>0.05$). The mean score of mothers in the difficulties of life and the impact of illness sub-dimension was found to be higher than that of the fathers and this difference was significant ($p<0.05$). The mean scores in the illness management and daily life of the child and parental agreement sub-dimensions were found higher in those parents with a university degree ($p<0.05$). On the other hand, the mean score in the difficulties of life and the impact of illness sub-dimension was lower in those parents with a degree and this difference was significant ($p<0.05$). It was also found that those parents whose income was higher than their expenses had relatively higher mean scores in the sub-dimensions of illness management and the daily life of the child and parent agreement, whereas they scored lower in the difficulties of life and the impact of illness sub-dimension and that these differences were significant ($p<0.05$). The study found that those parents with adequate knowledge of the illness had a higher mean score in the sub-dimension illness management and the daily life of the child with a significant difference ($p<0.05$). Those parents who received support from their social circles had higher mean scores in the sub-dimensions of illness management and the daily life of the child and parental agreement than those who did not receive any support ($p<0.05$) (Table II).

The difference between the children's gender, age, and the mean scores of the contact parent in the NPST sub-dimension was statistically insignificant ($p>0.05$). It was determined that the mean scores of both parents for the NPST and its sub-dimensions were similar ($p>0.05$). It was found that illiterate parents scored higher in the sub-dimension of information and communication support and their mean score had a significant difference ($p<0.05$). Parents with a university degree had a higher mean score in the emotional support sub-dimension and the mean total score of NPST and this difference with the other parents was significant ($p<0.05$). Those parents whose income was higher than their expenses had a higher mean score in the sub-dimensions of emotional support and respect support and this difference was significant ($p<0.05$). Those who were adequately informed about the illness had higher

Table I. Characteristics of parents and children (n=108)

Characteristics	n	%
Child's gender		
Female	42	38.9
Male	66	61.1
Child's age		
0-12 months	12	11.1
1-3 years	19	17.6
4-6 years	25	23.1
7-12 years	30	27.8
13-18 years	22	20.4
Interviewed parents		
Mother	88	81.5
Father	20	18.5
Education		
Illiterate	7	6.4
Literate without diploma	10	9.3
Primary school graduate	26	24.1
High school graduate	32	29.6
University degree	33	30.6
Income Level		
Income lower than expenses	42	38.9
Income equals expenses	56	51.8
Income higher than expenses	10	9.3
Information level on the illness		
Adequate	62	57.4
Partial	38	35.2
Inadequate	8	7.4
Support from social circle		
Received	49	45.5
Not received	59	54.5
Total	108	100

mean scores in the sub-dimensions of emotional support and respect support, as well as in the NPST overall and this difference was found to be significant (p<0.05). Those parents who received support from their social circle scored higher in the sub-dimensions of emotional support, providing quality care, and the total mean score of NPST and these differences were found to be significant (p<0.05) (Table III).

The three sub-dimensions of FaMM, which were modeled as a predictor of the NPST score account for 55.5% of the NPST score. There is a strong positive correlation

Table II. Comparison of parents' FaMM sub-dimension mean values according to certain child and parent characteristics (n=108)

	Illness management and the daily life of the child		**Difficulties of life and the impact of illness**		**Parental agreement**	
Characteristics	**$\bar{X}$**	**Ss**	**$\bar{X}$**	**Ss**	**$\bar{X}$**	**Ss**
Child's gender						
Female Male	3.01 2.99	0.59 0.67	3.73 3.82	0.58 0.65	3.73 3.70	0.82 0.77
t/p	0.223/0.824		-0.725/0.470		0.236/0.814	
Child's age						
0-12 months 1-3 years 4-6 years 7-12 years 13-18 years	2.97 2.85 2.94 3.05 3.12	0.55 0.52 0.69 0.64 0.73	3.80 3.88 3.86 3.71 3.69	0.68 0.46 0.63 0.66 0.69	4.03 3.85 3.45 3.64 3.80	0.81 0.66 0.86 0.79 0.73
F/p	0.554/0.696		0.434/0.784		1,474/0.215	
Contact parent						
Mother Father	2.96 3.16	0.61 0.73	3.85 3.49	0.59 0.71	3.68 3.87	0.82 0.59
t/p	1,231/0.221		**2,373/0.019***		-0.980/0.329	
Education						
Illiterate[1] Literate without diploma[2] Primary school graduate[3] High school graduate[4] University degree[5]	2.70 2.90 2.73 2.83 3.46	0.70 0.57 0.46 049 0.67	4.41 3.93 4.05 3.78 3.39	0.36 0.68 0.47 0.50 0.65	3.36 3.84 3.37 3.52 4.19	1.14 0.63 0.76 0.75 0.55
F/p	**8,119/0.001*** **5>1,3,4**		**7,989/0.001*** **3>5; 1>5**		**6,157/0.001*** **5>1,3,4**	
Income level						
Income lower than expenses[1] Income equals expenses[2] Income higher than expenses[3]	2.71 3.10 3.62	0.52 0.61 0.67	4.01 3.71 3.24	0.54 0.62 0.62	3.44 3.83 4.17	0.85 0.67 0.73
F/p	**11,440/0.001*** **3>2>1**		**7,747/0.001*** **1>2>3**		**5,074/0.008*** **3>2>1**	
Information level of illness						
Adequate Partial Inadequate	3.13 2.85 2.66	0.69 0.52 0.48	3.71 3.85 4.03	0.66 0.55 0.62	3.77 3.60 3.75	0.86 0.68 0.62
F/p	**3,565/0.032***		1,281/0.282		0.536/0.587	
Support from social circle						
Received Not received	3.17 2.85	0.67 0.57	3.68 3.86	0.68 0.56	3.92 3.54	0.77 0.76
t/p	**2,649**	**0.009***	-1,527	0.130	**2,535**	**0.013***

t= Independent t-test; F= One-way ANOVA
p<0.01*
FaMM: The Family Management of Childhood Chronic Conditions

Table III. Comparison of parents' NPST and sub-dimension mean values according to parents' identifying and illness-related characteristics (n=108)

	Information and communication support		**Emotional support**		**Respect support**		**Providing quality care**		**NPST- Total**	
Characteristics	$\bar{X}$	**Ss**	$\bar{X}$	**Ss**	$\bar{X}$	**Ss**	$\bar{X}$	**Ss**	$\bar{X}$	**Ss**
Child's gender										
Female	3.30	0.25	3.03	0.80	3.07	0.44	3.47	0.39	3.82	0.74
Male	3.36	0.31	2.90	0.82	3.08	0.56	3.46	0.38	3.67	0.86
t/p	-1.019/0.311		0.761/0.449		-0.122/ 0.903		0.164/0.870		0.925/0.357	
Child's age										
0-12 months	3.35	0.27	3.02	0.57	3.10	0.55	3.55	0.41	3.83	0.79
1-3 years	3.29	0.31	2.68	0.73	2.92	0.46	3.47	0.35	3.74	0.77
4-6 years	3.25	0.35	2.96	0.76	3.06	0.46	3.49	0.42	3.66	0.87
7-12 years	3.34	0.21	3.05	0.77	3.15	0.56	3.40	0.39	3.80	0.80
13-18 years	3.34	0.26	3.13	0.97	3.12	0.54	3.48	0.36	3.60	0.88
F/p	1,658/0.165		0.684/0.605		0.639/0.638		0.398/0.810		0.184/0.946	
Interviewed parents										
Mother	3.38	0.29	2.89	0.77	3.07	0.51	3.50	0.37	3.73	0.81
Father	3.30	0.29	3.25	0.94	3.10	0.52	3.33	0.42	3.75	0.86
t/p	0.630/0.530		-1,800/0.075		-0.203/0.839		1,792/0.076		-0.105/0.916	
Education										
Illiterate[1]	3.58	0.21	2.52	0.97	3.03	0.63	3.60	0.51	4.17	1.02
Without diploma[2]	3.33	0.25	2.9	0.58	3.17	0.54	3.54	0.34	3.46	0.64
Primary school[3]	3.40	0.30	2.64	0.67	3.02	0.51	3.43	0.38	3.43	0.77
High school[4]	3.25	0.28	2.78	0.65	2.92	0.42	3.43	0.40	3.44	0.77
University degree[5]	3.33	0.28	3.48	0.85	3.25	0.54	3.47	0.37	4.25	0.61
F/p	**2,506/0.047* 1>2,3,4,5**		**6,380/0.001* 5>1,3,4**		1,860/0.123		0.397/0.810		**7,337/0.001* 5>2,3,4**	
Income level										
Income lower than expenses[1]	3.38	0.28	2.72	0.67	2.91	0.45	3.41	0.35	3.52	0.78
Income equals expenses[2]	3.32	0.29	2.98	0.83	3.14	0.52	3.48	0.40	3.83	0.82
Income higher than expenses[3]	3.25	0.30	3.80	0.70	3.40	0.54	3.58	0.38	4.08	0.82
F/p	0.942/0.393		**8,050/0.001* 3>2>1**		**4,737/0.011* 3>1**		0.907/0.407		2,764/0.068	
Information level of illness										
Adequate	3.36	0.27	3.11	0.87	3.22	0.55	3.48	0.42	3.98	0.79
Partial	3.29	0.29	2.85	0.62	2.90	0.33	3.43	0.31	3.48	0.70
Inadequate	3.41	0.36	2.20	0.75	2.75	0.61	3.52	0.42	3.06	0.89
t/p	0.813/0.446		**5,147/0.007* 1>3**		**6,887/0.002* 1>2,3**		0.303/0.739		**8,197/0.001* 1>2>3**	
Support from social circle										
Received	3.30	0.31	3.09	0.88	3.17	0.56	3.55	0.39	4.11	0.70
Not received	3.37	0.27	2.84	0.74	2.90	0.46	3.39	0.37	3.42	0.78
t/p	-1,191/0.236		**1,620/0.108**		1,851/0.067		**2,156/0.033***		**4,795/0.001***	

t= Independent t-test, F= One-way ANOVA
p<0.01
NPST: Nurse Parent Support Tool

between the NPST scores and the illness management and the daily life of the child (AB1) and parental agreement (AB3) subdimensions and a strong negative correlation with the difficulties of life and the impact of illness (AB2) sub-dimension ($p<0.001$) (Table IV).

Discussion

Of the parents who participated in this study and provided care for their children, 81.5% were mothers (Table I). Similar studies with the parents of children with chronic illness show that the caregivers are mostly mothers (14,15). This may be due to the assumption that the role of caregiving in Turkish society is the responsibility of the mother rather than the father. It was found that 51.8% of the parents' income equaled their expenses. Among the parents, 57.4% stated that they were adequately informed about the illness and 54.5% that they did not receive support from their social circle (Table I). Similar studies show that more than half of the parents were well informed about the illness, received support from their social circles in caregiving but they were economically affected by their child's illness (8,14).

The difference between the gender and age of the children whose parents participated in this study and the mean sub-dimension FaMM scores was statistically insignificant (Table II). This shows that the parents' management of the existing condition is not affected by the age or gender of their child. In a similar study, the difference between the perceived stress and coping status of the parents and the child's gender and age variables were found to be statistically insignificant. Güneş Çalıcıoğlu and Uysal (16) and Kızıler et al. (17) reported that the age of the child does not affect the parent's coping level as a result of their study with the parents of children who had been diagnosed with cancer.

Table IV. Linear regression analysis predicting parents' scores in the FaMM sub-dimension of the NPST

Constant: NPST score	**B(b)**	**Standard Error for B**	**Beta (β)**	**T**	**p**
FaMM-AB1	12,665	2,999	0.472	5,309	0.001*
FaMM-AB2	-5,725	2,599	-0.290	-2,203	0.003*
FaMM-AB3	9,859	1,897	0.451	5,197	0.001*
		R	**R2**	**F**	**p**
		0.555	0.308	47,192	0.001*

FaMM-AB1: Illness management and the daily life of the child, FaMM-AB2: Difficulties of life and the impact of illness, FaMM-AB3: Parental agreement
*p<0.001
FaMM: The Family Management of Childhood Chronic Conditions, NPST: Nurse Parent Support Tool

The mean score of the mothers in the difficulties of life and the impact of illness sub-dimension was found to be higher than the fathers and this difference was significant (Table II). This result may be due to the fact that the care and treatment burden of the child in the hospital and at home are mostly undertaken by the mothers, as in the findings of this study. Similarly, the literature suggests that mothers display more submissive and helpless behavior in dealing with the problems associated with chronic illness in comparison to the fathers (17).

The mean scores in the illness management and daily life of the child and parental agreement sub-dimensions were found to be higher in those parents with a university degree (Table II). In one study, it was stated that the disease management scores of those mothers who had high school or higher education qualifications were higher (3). A similar study reported high mean care burden scores for those mothers with lower levels of education (15). This may be explained by the fact that those parents with higher levels of education have a better understanding of the information provided by the healthcare workers regarding the child's condition. Moreover, a higher level of education also means easier access to information from other sources.

It was also found that those parents whose income was higher than their expenses had relatively higher mean scores in the sub-dimensions of illness management and the daily life of the child and parent agreement; whereas they scored lower in the difficulties of life and the impact of illness sub-dimension (Table II). This may indicate that parents who have to struggle with their child's chronic illness have difficulty in meeting the needs of their child due to economic limitations, which in turn leads to increased stress. In another study on mothers caring for children with chronic illness, Özsoy (3) found that the child's chronic illness and daily life were more difficult to manage for those mothers with poor income as compared to those with moderate to high income levels. In another study conducted with the mothers of children receiving chemotherapy, it was found that as the level of income increased, the degree of anxiety in the mothers somewhat decreased (18). In a study conducted by Zhang et al. (11) in China to determine the factors affecting illness management in families with chronically ill children, it was found that those parents with lower income needed more family support.

This study found that those parents with an adequate knowledge of the illness had a higher mean score in the sub-dimension illness management and the daily life of the child with a significant difference (Table II). This finding

suggests that as a result of the information exchange with the parents about the child's illness, care, and the daily life impact, parents could continue their normal lives and see themselves as being more competent in illness management. Similarly, Taanila (19) found that those parents who received little information and practical advice about how to adapt to their child's chronic illness experienced five times more insecurity and helplessness than those who said they were adequately informed on these issues. Adaptation to the illness is a complex process for parents and being well-informed helped their well-being, adaptation, and coping. In another study conducted by Alahan et al. (14), the mean care burden score of those who were not well-informed about caregiving was found to be high.

Those parents who received support from their social circle had higher mean scores in the sub-dimensions of illness management and the daily life of the child and parental agreement than those who did not receive any support (Table II). It can be concluded that the more support received from the social circle, the more confident the parents felt in the daily life impact of the illness and the more they cooperated with each other. Similarly, the studies conducted by Tak and Mccubbin (20) showed that the more support the parents received from their social circle, the more capable they were in coping with the associated stress.

In the absence of support from nurses, parents can find themselves in crisis and they may try inappropriate methods of coping which can be detrimental to the short-term or long-term adaptation to the child's illness (21). In this study, it was determined that there was no difference between the gender, age, interviewed parents and nurse-given support score averages of the children (Table III). In a similar study, it was reported that child's gender did not make any difference in the mean scores in NPST (22). However, another study returned higher mean scores in the sub-dimensions of information and communication support and respect support for the parents of male children (23). This may be interpreted as a cultural difference whereby the gender of the child still bears some weight in some countries or population segments. In this study, it was determined that the mean scores of both parents for NPST and its sub-dimensions were similar (Table III). Contrary to the findings of this study, Sanjari et al. (9) found that fathers had a higher mean score in the sub-dimension of providing quality care in comparison to mothers.

It was found that illiterate parents scored higher in the sub-dimension of information and communication support and their mean score had a significant difference. Parents with a university degree had a higher mean score in the emotional support sub-dimension and the mean total score of their NPST and the difference with other parents was significant (Table III). In line with these finding, it can be suggested that each group had a stronger perception of the kind of support needed by them, as seen by the fact that illiterate parents needed information more than anything else since they had difficulty in accessing information regarding the illness, but those parents with a university degree needed more social circle support with regard to the illness and its daily life impact. Contrary to this result, Sanjari et al.'s (9) study shows that as the level of education increases, the mean score for the emotional support sub-dimension of the NPST decreases and there is no significant difference in the mean scores of the other sub-dimensions. In the study conducted by Yılmaz (24), it was determined that those parents who had just graduated from primary school had higher NPST scores. Another study found no difference between the parents' level of education and their mean total scores in NPST and its mean sub-dimension scores (25).

In this study, it was determined that the difference between the income levels of the parents and the total mean scores of the support given by the nurse was insignificant (Table III). These findings suggest that the average support provided by nurses in terms of information, emotion, respect, and care is perceived similarly by parents regardless of their economic and employment status. In their study, Akkoyun and Tas Arslan (25) reported that mothers with high income levels had lower total mean scores for NPST. However, some other studies showed no correlation between the parents' levels of income and their mean total scores for NPST and its sub-dimensions (9,25,26).

In the results of this study, it can be seen that the emotional support and respect support sub-dimension mean scores were also higher in addition to the NPST mean score of those parents who stated that they had knowledge about the disease (Table III). This result suggests that those parents who were adequately informed on the illness perceived better nurse-given support in terms of coping with the daily life impact of the illness and care of their children.

Those parents who received support from their social circle scored higher in the sub-dimensions of emotional support, and providing quality care, and also their total

mean scores of NPST (Table III). This suggests that nurse support is one of the most important factors in the concept of social support for parents.

In this study, it can be seen that there is a strong positive correlation between nursing support and the scores of illness management and the daily life of the child and parental agreement and a strong negative correlation with the difficulties of life and the impact of illness sub-dimensions (Table IV). Although there are no studies comparing nurse given support and disease management, similar studies have shown that support given by nurses plays an important role in the management of the disease for the child and the family (9-11). This result shows the positive effect of the nurses' support given to the parents on the daily life of the child's illness and on the relationship between the parents.

Study Limitations

This study was only conducted with the parents of child patients hospitalized in the PICU of a hospital and cannot be generalized to the universe.

Conclusion

In conclusion, the management of childhood chronic conditions improves in parallel with the parents' perception of nurse support. Therefore, it is of utmost importance for nurses to encourage parents to participate in the care of their child and help them understand the healthcare and treatment processes given to their child. It is also crucial to provide information in a straightforward manner and with clear language.

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Ethics

Ethics Committee Approval: This study was approved by the Okan University Ethics Committee (approval number: 96, date: 04.07.2018).

Informed Consent: The parents were informed about the research and their written consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: G.U., H.A., Data Collection and/or Processing: H.A., G.U., Statistical Analysis: H.A., G.U., Literature Review: G.U., H.A., Writing: G.U., H.A.

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Original Article

Which has an Influence on Mean Platelet Volume: Allergic Rhinitis or Asthma?

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ABSTRACT

Aim: Bronchial asthma and allergic rhinitis are mediated by similar allergic inflammatory mechanisms. Platelets play a role in allergic reactions which are inflammatory processes. The mean platelet volume (MPV) is a marker of platelet activation. This study aimed to investigate MPV value differences between children with allergic rhinitis during symptomatic or asymptomatic periods to determine whether MPV is a useful indicator of inflammation in allergic rhinitis.

Materials and Methods: The records of those patients with allergic rhinitis were analyzed retrospectively. Patients over two years of age who had complete blood count results from both their asymptomatic and the symptomatic periods were included in this study. Clinical characteristics (age, age at diagnosis, symptoms, and comorbid allergic diseases) and laboratory data (thrombocyte count, MPV, white blood cell count, eosinophil count, and percentage, immunoglobulin E level, and skin prick test results) were recorded from the patient files and the hospital registry system.

Results: MPV values during the symptomatic periods were statistically significantly higher than those from the asymptomatic period ($p<0.001$) in all patients. When the patients were grouped according to having asthma or not, MPV was found to be higher in the symptomatic period compared to the asymptomatic period in the group with asthma, but there was no difference between these two periods in the group without asthma ($p=0.017$, $p=0.102$ respectively). Additionally, MPV levels were significantly higher in the asthma group during both the symptomatic and the asymptomatic periods ($p=0.04$, $p=0.013$, respectively).

Conclusion: This study suggests that MPV cannot be used as an inflammation indicator in the symptomatic period for patients with allergic rhinitis. Asthma influences MPV values. It is recommended to conduct more detailed and prospective studies to show MPV inflammation in AR.

Keywords: Allergic rhinitis, asthma, children, mean platelet volume

Introduction

Allergic rhinitis is an immunoglobulin E (IgE) based inflammation in the nasopharynx which occurs in reaction to an allergen. In 1998, the Joint Task Force on Practice Parameters in Allergy, Asthma, and Immunology defined allergic rhinitis as an "inflammation of the membranes lining the nose and is characterized by nasal congestion, rhinorrhea, sneezing, itching of the nose, and/or postnasal drainage" (1). Within minutes of allergen exposure, preformed and newly synthesized mediators, including

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histamine, cysteinyl leukotrienes, prostaglandins, and platelet-activating factor, are released by mast cells (2).

Asthma is one of the most commonly seen diseases, affecting >300 million people worldwide. It is also common during childhood. Asthma and allergic rhinitis share similar allergic inflammatory mechanisms. Grossman (3) suggested that asthma and allergic rhinitis are "one airway, one disease". It has been shown that untreated rhinitis can increase the risk of asthma exacerbation by up to three times (4).

Platelets have been shown to play a role in various inflammatory diseases, including atherosclerosis, atherothrombosis, and asthma. Platelet activation markers such as Plasma β-thromboglobulin and platelet factor-4 have been reported to be elevated in symptomatic asthmatic patients (5). These mediators activate eosinophils, increase the expression of Fc-IgG and Fc-IgE receptors, and release histamine from the basophils (6).

Platelet volume increases as platelets are activated. Mean platelet volume (MPV) reflects the platelet size and can be used as an indicator of activated platelets. Changes in MPV values have been studied, especially in asthma cases (7,8). There are conflicting results about MPV values in allergic rhinitis, and to the best of our knowledge, there are limited studies on MPV in allergic rhinitis in children.

This study aimed to investigate MPV value differences between children with allergic rhinitis during their symptomatic and asymptomatic periods to determine whether MPV is a useful indicator of inflammation in allergic rhinitis. In addition, we planned to assess the effects of atopy, concomitant allergic diseases, and other factors on MPV values.

Materials and Methods

This study was performed at the Pediatric Allergy Departments of three hospitals. It was approved by the University of Health Sciences Turkey, İzmir Tepecik Health Practice and Research Center Non-Interventional Research Ethics Committee (date: 28.03.2019, no: 2019/5-2). The records of those patients with allergic rhinitis from January 2015 to September 2018 were analyzed retrospectively. Those patients who were over two years old at the time of admission, followed up for at least six months and who had complete blood count results from both their asymptomatic and their symptomatic periods were included in this study. The diagnosis and classification of allergic rhinitis were made according to the Allergic Rhinitis and its Impact on Asthma guidelines, 2016 (4). Clinical characteristics (age, age at diagnosis, symptoms, comorbid allergic diseases especially asthma) and laboratory data (thrombocyte count, MPV, white blood cell count, eosinophil count, and percentage, IgE level, and skin prick test results) were recorded from the patient files and the hospital registry system. The reference range for MPV was between 7.0 and 11 fL. In addition, the patients were classified into 2 groups; without asthma and asthma with allergic rhinitis. The diagnosis of asthma was made according to the Global Initiative for Asthma, 2018 guidelines criteria (9).

Skin prick testing was performed using a panel of common inhalant allergens (grass, weed and tree pollens, cat and dog dander, molds, Dermathophagoides pteronyssinus, and Dermathophagoides farinae) (Allergopharma, Reinbek, Germany). Saline and histamine solutions were used as the negative and positive controls, respectively. The results were evaluated after 20 minutes. A wheal with a diameter of 3 mm greater than the negative control was taken as a positive result.

Patients who did not meet the allergic rhinitis diagnostic criteria or who had missing laboratory data were excluded from this study.

Statistical Analysis

Data were evaluated using the Statistical Package for Social Sciences 21.0 (SPSS for Windows 21.0, Inc., Chicago, IL, USA). The results were expressed as frequency (percentage) for categorical data and mean ± standard deviation for numerical data with normal distribution or median (minimum-maximum and interquartile range) for numerical data without normal distribution. The independent samples t-test was used to compare the groups; the Wilcoxon test was used to compare any changes between groups. Spearman correlation analysis was used while investigating the association between variables. Any p-values <0.05 were considered statistically significant.

Results

A total number of 250 patients who met the inclusion criteria were included in this study. There were 141 males (56.4%), the mean age of the patients was 8.7±3.9 years and the mean duration of the symptoms was 3.0±2.2 years. One hundred thirty-six of the patients had (54.4%) perennial symptoms. Among the patients, 148 (59.2%) had asthma, 6 (2.4%) had a food allergy, 5 (2%) had urticaria, and 1 (0.4%) had atopic dermatitis. The patients' clinical and demographic data are shown in Table I.

In the comparison of the laboratory test results during the symptomatic and asymptomatic periods, MPV values during the symptomatic period were statistically significantly higher than those from the asymptomatic period (p<0.001). Serum IgE levels and eosinophil counts were also higher in the symptomatic group (p<0001) (Table II).

To investigate those factors affecting MPV, patients were grouped according to the presence of asthma and skin test positivity. MPV was found to be higher in the symptomatic period compared to the asymptomatic period in the group with asthma, but there was no difference between these two periods in the group without asthma (p=0.017, p=0.102 respectively).

Additionally, when we compared MPV levels between the group with asthma and without asthma, MPV levels were significantly higher in the asthma group during the symptomatic and the asymptomatic periods (p=0.04, p=0.013, respectively).

In the skin prick test positive group, MPV levels were higher during the symptomatic period than the asymptomatic period (p=0.005). However, in the skin prick test negative group, there were no significant differences between MPV levels during the symptomatic period and the asymptomatic period (p<0.05) (Table III).

In addition, it was observed that a weak negative correlation was found between MPV and the presence of asthma both in the symptomatic period (p=0.04, r=-0.13) and the asymptomatic period (p=0.013, r=-0.16), but there was no correlation between skin test positivity, IgE level, eosinophil number and percentage, and platelet counts (p>0.05) (data are not shown).

Table I. Demographic and clinical characteristics of the patients

Gender (M/F)	141/109
Age: (years) [median (min.-max.)]	8.0 (3-20)
Disease duration: (years) (median: min.-max.)	2.0 (1-15)
Prick test positivity: n (%)	222 (88)
Comorbid allergic disease: n (%)	
Asthma	148 (59.2)
Food allergy	6 (2.4)
Urticaria	5 (2.0)
Atopic dermatitis	1 (0.4)
No other	90 (36)

M/F: Male/female, min.-max.: Minimum-maximum

Table II. The comparison of the laboratory parameters of the patients during their symptomatic and asymptomatic periods

Laboratory parameters	During symptomatic period	During asymptomatic period	p-value
IgE (IU/mL)*	284 (29.7-388.5)	249 (23.3-330)	<0.001
Platelet count (x10^3)/mm^3*	325 (247-346)	313 (252-358)	0.397
MPV (fL)**	8.0 (7.2-8.8)	7.7 (7.0-8.6)	<0.001
Eosinophil count/mm^3*	389 (100-500)	255 (100-300)	<0.001
Eosinophil (%)*	4.7 (2.0-7.0)	2.7 (1.0-4.0)	<0.001

*Median (IQR)
**Mean ± SD
SD: Standard deviation, IQR: Interquartile range

Table III. The investigation of the factors affecting MPV levels

The factors	MPV levels during the symptomatic period (mean ± SD)	MPV levels during the asymptomatic period (mean ± SD)	p-value
The presence of asthma			
Yes	7.6±1.1	7.8 ±1.3	0.017
No	8.0±1.3	8.2±1.2	0.102
The skin prick test results			
Positive	7.7±1.2	7.9±1.3	0.005
Negative	7.9 ±0.8	8.0±0.8	0.439

MPV: Mean platelet volume, SD: Standard deviation

Discussion

In this study, we found that MPV values were higher during the symptomatic period than during the asymptomatic period in those patients with allergic rhinitis and asthma, but this was not seen in those patients with only allergic rhinitis. In the literature, it has been shown that platelets show the capacity to become activated upon local and systemic allergic reactions. Atopic individuals have higher levels of chemokines, β-thromboglobulin, and platelet factor 4 than healthy subjects after allergen exposure, which is evidence of an increase in thrombopoiesis and the role of platelets in airway inflammation (10). Animal models have shown that platelet activation plays an important role in the transmigration of circulating lymphocytes and eosinophils to the airways of allergic asthma (11). The high degree of platelet activation causes an increase in platelet volume. MPV reflects the platelet size. Therefore, higher MPV levels predict platelet activity and thus the intensity of the inflammation.

Kowal et al. (12) investigated platelet activation after exposure to house dust mites in asthmatic patients. They reported that prolonged airway inflammation after allergen exposure of asthmatic patients was related to intravascular platelet activation. Knauer et al. (13) showed significant changes in PF-4 levels in the circulation and the bronchoalveolar lavage of asthmatic patients after bronchial provocation via ragweed extract with a decline in FEV1. On the other hand, studies indicate no difference or lower values of MPV between asthmatic patients and healthy controls (7,14).

Allergic rhinitis is the most common atopic disease strongly associated with asthma. From the pathophysiological point of view, both bronchial asthma and allergic rhinitis are mediated by similar allergic inflammatory mechanisms. In the literature, there are studies indicating no changes in platelet activation in allergic rhinitis patients. Kasperska-Zajac and Rogela (15) investigated circulating platelet activity in patients with house dust mite sensitive allergic rhinitis who had either mild asthma or no asthma, and they found no difference in the platelet count or PF-4 and Beta-transforming growth factor levels from control patients. They also showed no increase in the plasma levels of chemokines in grass pollen allergic patients with just intermittent rhinitis during the grass pollen season (16).

Akgedik and Yağız (17) compared the MPV values of 250 adult patients. They divided these patients into three groups as only allergic rhinitis, only asthmatics, and having both asthma and allergic rhinitis. They found the lowest MPV values in those patients in the allergic rhinitis and asthma group. In contrast, we found higher MPV levels in the allergic rhinitis and asthma group during the symptomatic period. This difference may be due to our patients' asthma not being under control, and this inflammation may have affected their MPV levels.

Kasperska-Zajac et al. (18) also evaluated platelet activity measured by plasma PF-4 levels during the non-pollen season compared with the pollen season for patients with asthma-allergic rhinitis and a control group. They found plasma PF-4 levels in the patients' non-pollen season were significantly lower than their pollen season levels and did not differ significantly compared to the healthy subjects. They suggested that this might indicate that platelet activation within the systemic circulation is an important factor in developing seasonal allergic airway inflammation.

Chen et al. (19) observed that plasma PF-4 and beta-thromboglobulin protein levels decreased after one year's sublingual immunotherapy with house dust mite in allergic rhinitis children. In addition, this decrease is positively related to symptom scores. As immunotherapy modifies the allergic process, the inflammation reduces, and MPV levels decrease.

Study Limitations

The most important limitation of our study is its retrospective design. Also, we did not evaluate any control parameters of asthma during the symptomatic period of rhinitis. It is possible that their asthma was not under control, and this may have affected their MPV values. Since we did not have a control group, we cannot comment on the importance of MPV in those patients with allergic rhinitis. On the other hand, our study is important as few other studies have evaluated MPV levels in pediatric allergic rhinitis patients to date. It would be good to conduct more detailed (more patients, using an asthma control test) and prospectively designed studies to show MPV inflammation in AR.

Conclusion

It was observed that MPV levels did not differ between the symptomatic and asymptomatic periods in those patients with only AR but they were higher in those patients with both asthma and allergic rhinitis during the symptomatic period. Therefore, it was thought that MPV could not be used as an inflammation indicator in the symptomatic period for patients with allergic rhinitis alone.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, İzmir Tepecik Health Practice and Research Center Non-Interventional Research Ethics Committee (date: 28.03.2019, no: 2019/5-2).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.D.Ş., E.E.Ö., Ö.S., M.D., T.T., Concept: H.D.Ş., Ö.S., T.T., Design: H.D.Ş., E.E.Ö., Ö.S., M.D., T.T., Data Collection and/or Processing: H.D.Ş., E.E.Ö., Ö.S., M.D., T.T., Analysis and/or Interpretation: H.D.Ş., T.T., Literature Search: H.D.Ş., T.T., Writing: H.D.Ş., T.T.

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Original Article

Continuous EEG Monitoring in Critically Ill Children and Prognostic Factors for Short-term Outcome: An Observational Study

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ABSTRACT

Aim: To evaluate the association of etiology, continuous electroencephalography (cEEG) findings and neuroimaging findings with short-term outcomes for patients admitted to a pediatric intensive care unit (PICU) for acute encephalopathy.

Materials and Methods: A total of 24 children admitted to a PICU for acute encephalopathy were enrolled into this study. The etiology, treatment, duration of stay in the PICU, their demographic information and their past medical history were recorded. cEEG was initiated as quickly as possible following admission to the PICU and continued for at least 24 hours. Their short-term prognosis was evaluated by the Pediatric Cerebral Performance Category score (PCPC) at PICU discharge.

Results: The most common cause was traumatic brain injury comprising 25% (n=6) of all cases. Other common causes were asphyxia (hanging, foreign body aspiration, drowning) (n=4, 16.67%) and intoxication (n=3, 12.5%). Twenty-two patients underwent cranial imaging. The most common findings in CT were hemorrhage (n=6, 30%) and ischemia/edema (n=6, 30%). Fourteen patients had unfavorable PCPC outcome scores. There was a tendency for poorer outcomes in those patients with hemorrhage/fracture or ischemia/edema in the imaging and for those patients who needed either pre-hospital CPR or had non-convulsive seizures but without statistical significance.

Conclusion: cEEG in critically ill children is useful for detecting both epileptic and non-epileptic events. The use of cEEG in PICUs can be helpful for the better management of cases.

Keywords: Acute encephalopathy, children, continuous EEG monitoring, intensive care, prognosis

Introduction

Acute encephalopathy is responsible for 2-3% of pediatric emergency department visits and 1-11% of pediatric intensive care unit (PICU) admissions (1,2). Acute encephalopathy is an important cause of morbidity and mortality. Prompt and proper evaluation and treatment are of the utmost importance. Even though it has a low sensitivity for defining the underlying etiology, electroencephalography (EEG) is a valuable tool in determining the extent of cerebral injury and long-term prognosis.

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Non-convulsive seizures (NCS) and non-convulsive status epilepticus (NCSE) are common in critically ill children, occurring in 10-50% of patients with acute encephalopathy (3). Pediatric patients may be at higher risk of NCS when compared to adults due to lower seizure thresholds, limited communication, and various behavioral disturbances, making the diagnosis of NCS more challenging and suggesting the need for closer monitoring in this population (4). Additionally, there is increasing data that electrographic seizures and electrographic status epilepticus are associated with worse outcomes (3,5).

Continuous EEG (cEEG) monitoring can lead to changes in the clinical management of patients in PICUs, including the initiation, escalation or discontinuation of anti-seizure drugs or urgent neuroimaging (6).

The aim of this study was to evaluate the association of factors such as etiology, cEEG findings and neuroimaging findings with the short-term outcome of those patients admitted to a PICU with acute encephalopathy.

Materials and Methods

Twenty-four patients admitted to Ege University Faculty of Medicine, PICU due to acute encephalopathy with a Glasgow Coma Scale score of eight or less, between 01.05.2018 and 01.10.2018 were included in this study prospectively. Their etiology, treatment, duration of stay in the PICU, demographic information, neuroimaging results and past medical history were recorded. cEEG was initiated as quickly as possible following admission to the PICU and continued for at least 24 hours. All recordings were carried out as outlined by the international 10-20 system with an electrode cap. Electrodes were applied using a conductive paste. All acquisitions were performed by the same technician using the same device (Brain quick clinical EEG line Micromed s.p.a.Italy). cEEG evaluation was made in accordance with the American Clinical Neurophysiology Society's (ACNS) Standardized Critical Care EEG Terminology (7).

EEG traces were evaluated in terms of background activity (predominant frequency, symmetry, voltage, continuity), and the presence of stage II sleep transients (K-complexes and spindles), periodic discharges (PDs), rhythmic delta activity (RDA) and interictal discharges. Electrographic seizures are defined as abnormal, paroxysmal electroencephalographic events that differ from the background activity, last longer than ten seconds (unless associated with clinical signs), have a plausible electrographic field, an evolution in frequency, morphology and spatial distribution. Electrographic status epilepticus is defined as uninterrupted electrographic seizures lasting 30 minutes or longer, or repeated electrographic seizures totaling more than 30 minutes in any one-hour period (8).

cEEG recordings were reviewed every eight to twelve hours by a child neurologist. In case where frequent NCS were identified, more frequent interpretations were provided until seizures were controlled. If clinical events were recorded, cEEG was interpreted as soon as possible whether that event was ictal or non-ictal. In all cases, cEEGs were recorded for at least 24 hours. In case of convulsive/NCS or abnormal background activity (discontinuous or burst suppression), cEEG monitoring was extended to 72 hours. cEEG recording was continued for at least six hours following the last seizure. The first hour of the cEEG (cEEG 1 h) and rest of the recording (cEEG 24 h) were evaluated separately.

Clinical and electrographic seizures were treated with intravenous midazolam or levetiracetam.

EEGs were evaluated by six independent readers (three senior child neurologists, two junior child neurologists, one pediatric resident) in accordance with the ACNS Standardized Critical Care EEG Terminology (7). Interrater agreement was assessed as a percentage of perfect agreement and Fleiss' kappa among the six reviewers (9).

The Pediatric Cerebral Performance Category score (PCPC) at PICU discharge was determined in every case. The PCPC is a validated six-point scale categorizing degrees of functional impairment. PCPC categories are: 1= normal, 2= mild disability, 3= moderate disability, 4= severe disability, 5= coma and vegetative state, and 6= death (10). PCPC scores of 3-6 (moderate/severe disability, vegetative, death) were accepted as unfavorable short-term outcomes.

Statistical Analysis

Data analysis was performed in Ege University Faculty of Medicine Department of Biostatistics. The SPSS (Statistical Package for Social Sciences) for Windows 25.0 package program was used for statistical analysis. Numerical variables are presented as arithmetic mean ± standard deviation or median (minimum-maximum); categorical variables are presented as summary statistics as numbers and percentages. The normality of the data in numerical variables was tested with the Shapiro-Wilk test. For numerical variables without normal distribution, Wilcoxon analysis was used in paired groups. In case of materiality, binary comparisons were made with Dunn's test. For categorical data, the comparison between groups was made

by creating cross tables using chi-square analysis. All data analysis was performed at the 0.05 significance level.

This study was reviewed and approved by Ege University Faculty of Medicine Ethics Committee (date: 08.05.2018, approval no: 18-5/49). The purpose of this study was explained to the legal guardian of every patient. Written informed voluntary consent was obtained from all individual participants included in this study. This study adhered to the ethical guidelines and was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki.

Results

Patient Characteristics & cEEG Findings

Of the 24 patients included in this study, 14 were female (58%) and 10 were male (42%). The mean age of the patients was 92.24±69.5 months (4-216 months).

The average time to reach an emergency setting was 142.5±93.3 minutes (40-270 minutes). The average time to start cEEG acquisition after PICU admission was 124.8±61.07 minutes (30-240 minutes). The mean cEEG monitoring duration was 1,620±907.01 minutes (1,080-4,320 minutes). cEEG recordings lasted 24 hours for 21 patients. In two patients with a burst suppression pattern (BSP) and NCS (case 7 and case 21) and one patient with convulsive and NCS (case 23) cEEG monitoring was extended to 72 hours. All the patients were orotracheally intubated and mechanically ventilated during the monitoring period. The length of stay in the PICU was between two and 46 days (mean 13.75±11.6 days).

Cardiopulmonary resuscitation (CPR) was applied in four cases before admission to the hospital. Four patients presented with seizures before admission to the PICU. Only one patient (case 4) had a seizure during the first hour of cEEG monitoring, which lasted for two minutes. The patient had three more focal onset myoclonic seizures lasting 1-2 minutes in cEEG 24 h. The seizures were successfully treated with intravenous midazolam.

The most common cause for admission was traumatic brain injury (TBI) comprising 25% of all cases (n=6). Other common causes were asphyxia (hanging, foreign body aspiration, drowning) (n=4, 16.67%) and intoxication (n=3, 12.5%). The etiology and clinical information regarding the cases are presented in Table I.

Twenty patients underwent cranial computed tomography (CT). Cranial magnetic resonance imaging (MRI) was also obtained in 10 out of the 20 cases with CT scan. Two patients were evaluated with MRI alone and no neuroimaging was possible in two patients. The most common findings in CT were hemorrhage (n=6, 30%) and ischemia/edema (n=6, 30%). Hemorrhage (33.33%), ischemia/edema (25%), diffuse axonal injury (16.67%) and T2 hyperintensities with restricted diffusion (16.67%) were the common findings on cranial MRI. The demographic, radiological and cEEG findings are presented in Table I.

The cEEG data of the 24 patients included in this study were analyzed in two different categories: The first hour of monitoring (cEEG 1 h) and after the first hour (cEEG 24 h). The cEEG 1 h and 24 h findings are presented in Table II.

Slow background activity (theta and/or delta) was observed in 15 cases (63%) in cEEG 1 h and 17 out of 24 cases (70%) in cEEG 24 h. The rate of slow background activity during the first hour and after the first hour recordings were similar (63% vs. 70%) (p=0.54).

NCSs were detected in two patients (8%) within the first hour of monitoring. Case 21 with suspected metabolic encephalopathy had an NCS lasting 50 seconds. Case 23 who also had a myoclonic seizure had an NCS lasting 60 seconds in the first hour of cEEG. Both seizures terminated spontaneously. Four patients had NCSs in cEEG 24 h. Two of these (case 21 and case 23) also had NCSs in the first hour of recording. Case 23 had four NCSs in cEEG 24 h, none of which were longer than two minutes. Case 21 had one NCS during the recording after the first hour. Case 7, admitted for drowning, had one NCS during cEEG 24 h. Case 17, admitted for head trauma, had three NCSs in cEEG 24 h lasting 1-2 minutes. None of the patients with NCS received paralytic medication infusion. When all of the patients were evaluated, two (18%) of all the NCSs were detected in cEEG 1 h, while 9 (82%) were detected in cEEG 24 h.

Two out of four patients with NCS were less than six months of age, one was eight years old and the other was 11 years old. NCS was not observed in the patient with a previous epilepsy diagnosis. Two of the four patients with NCS were admitted for head trauma, one for asphyxia and one for metabolic disease.

NCSE was not detected in any of the patients.

Short-term Outcome (PCPC)

In terms of PCPC scores at PICU discharge, 10 cases had favorable short-term outcomes (score ≤2) and 14 cases had unfavorable outcomes (score ≥3). One patient (case 7) was lost on the 13th day of his admission to the PICU. This patient had a history of CPR for 20 minutes after drowning.

Table I. Etiology, neuroimaging and electroencephalographic properties of the cases

Patient	Age (months)	Etiology	Imaging finding	EEG finding (0-1 hour)	EEG finding (2-24 hours)	Prognosis (PCPC score)
1	147	Asphyxia (hanging)	Ischemia/edema (CT)	*	RDA IED	Unfavorable (4)
2	49	Hepatic encephalopathy	Not performed	TWs RDA	*	Favorable (2)
3	22	TBI	Hemorrhage (CT) Hemorrhage, DAI (MRI)	IED	RDA IED	Unfavorable (3)
4	166	Epilepsy	Normal (CT, MRI)	IED	*	Favorable (2)
5	98	TBI	Hemorrhage (CT) Hemorrhage, DAI (MRI)	Amplitude asymmetry (mild)	Amplitude asymmetry (mild)	Favorable (2)
6	125	Intoxication (butane abuse)	Ischemia/edema (CT, MRI)	*	*	Unfavorable (4)
7	98	Asphyxia (drowning)	Ischemia/edema (CT)	BSP	BSP NCS	Unfavorable (6)
8	27	Asphyxia (foreign body aspiration)	Normal (CT)	RDA	IED	Unfavorable (3)
9	11	Metabolic encephalopathy	Ischemia/edema (CT, MRI)	*	RDA	Unfavorable (4)
10	34	Hypertensive encephalopathy (PRES)	Cerebral atrophy (CT) T2 hyperintensities with restricted diffusion (MRI)	Discontinuous activity IED	BSP	Favorable (2)
11	36	TBI	Hemorrhage, fracture, ischemia/edema (CT) Hemorrhage, ischemia/edema, subfalcine herniation (MRI)	*	IED	Unfavorable (4)
12	126	ADEM	Demyelinating lesions (MRI)	*	*	Favorable (1)
13	190	Intoxication (attempted suicide)	Normal (CT)	IED	IED	Favorable (1)
14	40	Asphyxia (drowning)	Not performed	Amplitude asymmetry (marked)	*	Unfavorable (4)
15	216	Intracranial mass	Hemorrhage (CT)	*	*	Unfavorable (4)
16	216	Fanconi anemia (septic shock, MOF)	Normal (CT)	BSP	Discontinuous activity	Unfavorable (4)
17	134	TBI	Hemorrhage, fracture (CT)	*	IED NCS	Unfavorable (3)
18	40	Uremic encephalopathy (HUS)	Extrapontine myelinolysis (CT, MRI)	Discontinuous activity	Discontinuous activity	Favorable (2)
19	187	Intoxication (attempted suicide)	Normal (CT)	*	*	Favorable (1)
20	138	TBI	Normal (CT)	Frequency asymmetry (mild)	*	Favorable (1)
21	5	Metabolic encephalopathy	T2 hyperintensities suggestive for metabolic disease (MRI)	NCS	Frequency asymmetry (mild) IED NCS	Unfavorable (3)
22	76	Hepatic encephalopathy	Normal (CT)	Amplitude asymmetry (mild)	Amplitude asymmetry (mild)	Favorable (2)

Table I. Continued

Patient	Age (months)	Etiology	Imaging finding	EEG finding (0-1 hour)	EEG finding (2-24 hours)	Prognosis (PCPC score)
23	4	TBI	Hemorrhage, ischemia/ edema (CT, MRI)	Amplitude asymmetry (marked) LPD RDA IED CS, NCS	Discontinuous activity LPD, BIPD RDA CS, NCS	Unfavorable (4)
24	11	CINCA syndrome	Cerebral atrophy (CT, MRI)	IED	*	Unfavorable (3)

ADEM: Acute disseminated encephalomyelitis, BIPD: Bilateral independent periodic discharges, BSP: Burst suppression pattern, CINCA syndrome: Chronic infantile neurologic cutaneous and articular, CS: Convulsive seizure, CT: Computed tomography, DAI: Diffuse axonal injury, IED: Interictal epileptiform discharges, LPD: Lateralized periodic discharges, MOF: Multi organ failure, MRI: Magnetic resonance imaging, NCS: Non-convulsive seizure, PCPC: Pediatric cerebral performance category, PRES: Posterior reversible encephalopathy syndrome, RDA: Rhythmic delta activity, TBI: Traumatic brain injury, TWs: Triphasic waves
*: No pathological finding

The scores of all four cases with a history of CPR before the hospitalization was 3 or above.

There were not enough subjects in all groups to reliably test the relationship between etiology and prognosis statistically. However, those patients with asphyxia, head trauma or metabolic disease tended to have worse prognosis. The etiology and PCPC scores of the cases are outlined in Table I.

When the relationship between cranial imaging findings and short-term outcome was evaluated, all of the patients with "ischemia/edema" in cranial imaging and 83.3% (5/6) of those patients with "hemorrhage±fracture" displayed unfavorable outcome. The difference was statistically significant for the ischemia/edema group but not for the hemorrhage±fracture group (p=0.046, p=0.333). Additionally, having a normal cranial imaging was not related to favorable outcome (p=0.074). The cranial imaging findings and short-term outcome results are outlined in Table III.

When the short-term outcome was evaluated in relationship to the frequency of cEEG background activity, the outcomes of all patients with alpha (including beta) frequency was good and the outcomes of those patients with a slowing of background activity was variable. In the latter group, five out of 13 patients (38%) displayed good outcome.

Out of four patients with discontinuous background activity, two had favorable and two had unfavorable outcomes. Two of the three patients with BSP had unfavorable outcomes. One patient (case 7) with burst suppression was lost.

When evaluated in terms of background properties (frequency, continuity, presence of sleep characteristics, presence of episodic or rhythmic activity) and short-term prognosis, the data was either not suitable for statistical analysis or did not reach statistical significance.

All four patients with NCS had unfavorable outcomes but the difference did not reach statistical significance (p=0.115).

Four patients had NCS. Two of these patients had NCS in both cEEG 1 h and cEEG 24 h. Whereas two patients had NCS only in cEEG 24 h. Nine out of 11 NCS in the study were recorded in cEEG 24 h. Patients with ischemia/ edema in cranial imaging had significantly worse prognosis. Although those patients with asphyxia, head trauma and metabolic disease and those patients who received CPR before hospitalization tended to have worse prognosis, the differences were not statistically significant.

Discussion

Acute encephalopathy can be traumatic or non-traumatic. Common etiological causes and prognosis vary according to age and the quality of care provided. In a study by Löhr Junior et al. (11), the causes of acute coma in children were as follows; central nervous system (CNS) infection in 30%, status epilepticus in 23%, hypoxic ischemic encephalopathy in 22%, toxic metabolic causes in 18%, and other causes in 8% of the patients. In the study by Schreiber et al. (12) which included 94 children, the most common causes for acute encephalopathy were prior neurologic problems in 27.7%, TBI in 17%, meningitis/encephalitis in 16% and hypoxia/anoxia in 11.7% of the children. In our study, TBI was found to be the cause for acute encephalopathy in 6 cases (25%). Other causes were asphyxia (16.67%), intoxication (12.25%), hepatic encephalopathy (8.33%), metabolic encephalopathy (8.33%), uremic encephalopathy (4.17%), hypertensive encephalopathy (4.17%), septic shock

(4.17%), chronic infantile neurologic cutaneous articular syndrome (4.17%), intracranial mass (4.17%), acute disseminated encephalomyelitis (4.17%), and epilepsy (4.17%). In our study, TBI was the most common etiological reason (p=0.024). This might be related to our PICU being a tertiary trauma center which serves a wide region. None of the patients included in this study had CNS infection, which is common in other studies.

NCS and NCSE have been shown to develop in 10-40% of patients admitted to PICUs with acute encephalopathy. Approximately half of electrographic seizures develop within the first hour and 80-90% within the first 24 hours (5,13-15). Jette et al. (15) reported the incidence of NCS as 39% in a four-year study in 117 children who were under the age of 18 and hospitalized in a PICU. While 15% of these seizures developed in the first hour of recording,

Table II. Cranial imaging and short-term outcome findings in patients

			cEEG 1 h (number of patients)	**cEEG 24 h (number of patients)**
Slow background activity*			15	17
Continuity*	Continuous		20	19
	Discontinuous		2	3
	Burst suppression pattern		2	2
Sleep structure	Stage 2 sleep transients present		9	15
Asymmetry	Amplitude	Mild Marked	2 2	2 -
	Frequency	Mild Marked	1 -	1 -
Periodic & rhythmic discharges	Lateralized periodic discharges		1	2
	Rhythmic delta activity		3	4
	Triphasic waves		1	
IED	Spike		1	1
	Sharp		6	7
Seizure	Convulsive seizure		1	1
	Non-convulsive seizure		2	4

IED: Interictal epileptic discharge
*: Some patients had more than one pattern throughout the acquisition

Table III. Cranial imaging and short-term outcome findings in patients

Imaging finding	**Patients (n, %)**	**Favorable prognosis (n, %)**	**Unfavorable prognosis (n, %)**
Hemorrhage/fracture	6 (27.27)	1 (16.67)	5 (83.33)
Ischemia/edema	6 (27.27)	-	6 (100)
Cerebral atrophy	2 (9.09)	1 (50)	1 (50)
Diffuse axonal injury	2 (9.09)	1 (50)	1 (50)
Demyelinating lesions	1 (4.54)	1 (100)	-
Extrapontine myelinolysis	1 (4.54)	1 (100)	-
Subfalcine herniation	1 (4.54)	-	1 (100)
T2 hyperintensities with restricted diffusion	1 (4.54)	1 (100)	-
T2 hyperintensities suggesting metabolic disease	1 (4.54)	-	1 (100)
Normal	7 (31.81)	5 (71.43)	2 (28.57)

*: Twenty-two patients underwent cranial imaging. Some patients had more than one finding

80% developed within 24 hours. In a prospective study conducted by Schreiber et al. (12) with 94 children with acute encephalopathy, NCSs were detected in 30% and NCSE in 18% of patients. Ninety-seven percent of these seizures were detected during 24 hour monitoring. In the study by Abend et al. (14), 101 children and infants who were admitted to a PICU for altered states of consciousness were evaluated. Thirty-two percent of the patients had NCSs and 19% had NCSE. Fifty-two percent of these seizures were detected in the first hour and 87% of them were detected in 24 hour cEEG monitoring (6). Similar to previous studies, only 18% (2/11) of NCSs developed within the first hour of recording in our group. The rest of the NCSs were observed within the 23 hours after the first hour. In three cases, monitoring continued for 72 hours and no seizures were detected after 24 hours. In a retrospective study which included 625 adult patients monitored in a tertiary center, 72 h risk of seizures were found to be lower than 5% if no epileptiform abnormalities were present in the first two hours of recording (16). Children may be at increased risk for NCS compared to adults (17). Younger age, prior convulsive status epilepticus or seizures and acute neuroimaging abnormalities were reported as risk factors for having NCS in critically ill children (3,18-20). In our study, TBI was found to increase the risk of NCS significantly (p=0.032).

Acute brain injury is reported to be associated with worse outcome in the literature (5,12). The study by Fink et al. (21) included 130 children with infectious encephalopathy or TBI in Africa. Patients with TBI were reported to have worse outcome than infectious encephalopathy. In the present study, the short-term outcome was unfavorable in asphyxia, TBI, and inborn metabolic diseases groups for 75%, 66.6% and 100% of cases, respectively. However, the correlation between the etiology and short-term outcome did not reach statistical significance. This might be due to the small sample size of our group.

It is well established that cranial imaging is useful for diagnosis in acute encephalopathy. Additionally, it may help in predicting the prognosis (22,23). In this study, we found that having ischemia/edema in cranial imaging to be a significant risk factor for unfavorable short-term outcome (p=0.046). Although those patients with hemorrhage/ fracture in cranial imaging also had unfavorable outcome, the difference did not reach statistical significance (p=0.333). This was thought to be due to our small sample size.

Some studies have demonstrated that patients with severe EEG background abnormalities such as discontinuous activity and BSP tend to have worse prognosis than those patients with mild/moderate background abnormalities (5,24). Topjian et al. (24) evaluated 128 patients who underwent EEG monitoring within one day of return of spontaneous circulation in terms of cEEG background activity, EEG reactivity and PCPC scores. EEG background pathologies including slow-disorganized, discontinuous-burst suppression, attenuated-flat activity and an absence of EEG reactivity were associated with mortality and unfavorable neurologic outcome. It is plausible to expect worse prognosis in those patients with severe background abnormalities such as BSP. However, due to the small sample size and low number of patients in each group, we could not make a statistical statement.

Some studies have shown an association between electrographic seizures/ electrographic status epilepticus and unfavorable neurodevelopmental outcome in critically ill children (5,12,25-27). Kirkham et al. (25) performed cEEG (one to three channels) in 204 children aged ≤15 years and determined their outcome at 1 month. They reported that unfavorable outcome (29/111 survivors; 26%) was independently predicted by the presence of electroencephalographic seizures. A recent study which included data from the PANGEA study stated that receiving anti-seizure medication was associated with worse neurological outcomes (27). In our study, although there was a tendency for poorer outcome in those patients with NCS, the difference did not reach statistical significance. This might be due to the small sample size of our study.

Study Limitations

There are limitations in our study. First, we had a small sample size. Additionally, our study was not sufficiently powered. This may have caused us to report some factors as being not significantly related with outcome which may actually be seen to be significant with a larger sample size. The strength of this study is that all EEG recordings were evaluated by six interpreters and interrater agreement rates were assessed with statistical methods. We think that this data may be more useful when pooled with other data found in the literature.

Conclusion

In conclusion, cEEG in critically ill children is useful not only for detecting NCS but also for defining other non-epileptic events. The use of cEEG in PICUs can contribute to the more exact management of cases. Optimum collaboration between intensive care and neurology units is needed.

Ethics

Ethics Committee Approval: This study was reviewed and approved by Ege University Faculty of Medicine Ethics Committee (date: 08.05.2018, approval no: 18-5/49).

Informed Consent: Written informed voluntary consent was obtained from all individual participants included in this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Design: Ö.Ö.B., Data Collection and/or Processing: Ö.Ö.B., P.Y.Ö., Analysis and/or Interpretation: Ö.Ö.B., P.Y.Ö., Revising the Article: P.Y.Ö., S.K., İ.D., H.M.S., S.Y., G.A., H.T., B.K., S.G., Writing: Ö.Ö.B., E.Ş., S.G.

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Original Article

Maternal Concerns Regarding Chewing Dysfunction in Children with Cerebral Palsy

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ABSTRACT

Aim: The aim of this study was to investigate the concerns of those mothers with children with cerebral palsy (CP) who were referred for a chewing evaluation, and the relationship between their chewing performance levels and the concerns of their mothers.

Materials and Methods: A total of 55 children with CP, and their mothers were included in this study. Age, gender, height, weight, and type of CP were noted. The Karaduman Chewing Performance Scale (KCPS) was used to define the chewing performance level. Children with a KCPS level of 0 were categorized as "children without chewing dysfunction", and children with KCPS level 1 to IV were defined as "children with chewing dysfunction". The Turkish version of the Feeding/Swallowing Impact Survey (T-FS-IS) was used to evaluate the maternal concerns relating to the child's feeding and swallowing problems.

Results: The mean age of children was 4.45±2.56 (minimum=2, maximum=11) years, of which 58.2% were male. There was a moderate to strong correlation between the KCPS and daily activities, worry, feeding difficulties and the total score from the T-FS-IS ($p<0.001$, $r=0.71$, $r=0.64$, $r=0.72$, $r=0.74$, respectively). The mothers of those children with chewing dysfunction reported more problems in the total score and all subscales of the T-FS-IS than those mothers of children without any chewing dysfunction ($p<0.01$).

Conclusion: This study suggests that the chewing performance levels of children were associated with their mothers' concerns, and those mothers of children with CP who had chewing dysfunction have higher concerns relating to feeding-swallowing difficulties. This knowledge regarding maternal perception indicates that clinicians should consider the concerns of the mothers during the management of chewing dysfunction.

Keywords: Child, cerebral palsy, parent, concern, chewing dysfunction

Introduction

Cerebral palsy (CP) is a group of permanent disorders of movement and posture causing physical disability in childhood. In addition, children with CP may experience several disabilities including cognitive problems, hearing and visual abnormalities, communication disorders, gastrointestinal problems and feeding difficulties (1).

Feeding is an important function for well-being and health throughout life, especially in childhood. Children with CP commonly have feeding difficulties, which may cause inadequate growth, inappropriate nutritional status, prolonged mealtimes, delayed oral feeding skills, and respiratory problems (2). Chewing dysfunction is one of the most important feeding difficulties seen in children with CP (3,4). It can lead to an inability to intake any solid food (5,6),

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and may cause insufficient obtainment of the necessary nutrition and hydration. Therefore, chewing dysfunction can affect growth and general health, and also result in stressful interactions between children and their parents (7). Therefore, chewing dysfunction in children with CP can affect both the child and their parents.

Family participation and motivation is very important in the management of feeding difficulties. In particular, mothers experience difficulties during caring for a child who has feeding and swallowing difficulties, which often cause a heavy burden (8,9). There are several factors to consider including coping with mealtime challenges, participating in medical and rehabilitative treatments and supporting the educational aspect of the child. Thus, having a child with feeding difficulties is a stressful situation for the parents (8-11). Increased anxiety levels in parents decreases their competence, and was found to be associated with less responsive feeding practices (12). Therefore, it is important to define parental concerns regarding their children with CP who have chewing dysfunction. However, to the best of our knowledge, the concerns of the mothers of children with CP relating to their chewing dysfunction and its impact on their quality of life had not been previously examined. We aimed to investigate the concerns of the mothers of children with CP who suffer from chewing dysfunction, and the relationship between the chewing performance levels and the concerns of the mothers.

Materials and Methods

The present study was conducted at a department of physical therapy and rehabilitation at a university hospital. This study was approved by the Non-invasive Clinical Research Ethics Committee of the Hacettepe University (approval number: GO21/206, approval date: 23.02.2021). A written informed consent form in accordance with the Declaration of Helsinki was obtained before enrollment.

Participants

Children who (i) were diagnosed as CP, (ii) were above the age of 2 years, (iii) had full oral feeding, (iv) were referred for a chewing evaluation, and their mothers were included in this study. The demographic information of the children including their age and gender, anthropometric measurements including height and weight, and their type of CP were recorded. Height-for-age (HAZ) and weight-for-age (WAZ) scores as nutritional indicators were calculated using the World Health Organization (WHO) Anthro Plus software (13).

Evaluation Procedures

The gross motor functional level was determined using the Gross Motor Function Classification System (GMFCS) (14). It is a standardized system to classify the functional motor levels of children in terms of five levels. GMFCS level 1 describes the most independent functional motor level, and GMFCS level 5 describes the most dependent functional motor level (14). An increasing level indicates a higher level of dependence.

Feeding related descriptive information including transition time to additional and solid food, duration of mealtimes, number of meals, initial teething time, number of teeth, and the food consistencies which the child could consume were recorded.

The chewing performance level was determined using the Karaduman Chewing Performance Scale (KCPS) (15). The KCPS is a five level classification system which is used to determine chewing performance levels in children. Increasing levels indicate decreased chewing performance levels. Level 0 refers to normal chewing function, and level 4 refers to no biting or chewing.

The children were positioned in a sitting position, and a standard biscuit was presented in front of their mouth for them to bite on and chew. An experienced physical therapist scored the chewing performance levels of the children using the KCPS. Those children with KCPS level 0 were categorized as "children without chewing dysfunction", and children with KCPS levels of 1 to IV were categorized as "children with chewing dysfunction".

The maternal concerns relating to the child's feeding and swallowing problems were evaluated by means of the Turkish Version of the Feeding/Swallowing Impact Survey (T-FS-IS) (16,17). The T-FS-IS is a parent report instrument to measure the effects of feeding and swallowing problems on the quality of life of the caregivers. It has 18 questions with three major categories, namely "daily activities", "worry", and "feeding difficulty". Each question is answered on a 5-point Likert scale ranging from 1 (never) to 5 (almost always). An average score for each subscale and an average total score are calculated, and higher scores show higher levels of concerns relating to feeding-swallowing difficulties.

Statistical Analysis

Statistical power analysis was performed using G*Power. A total of 55 children with CP, and their mothers have a 0.5 effect size, 5% type 1 error margin, and 81% statistical power conditions to detect the relationship between the chewing

performance levels of the children and the concerns of their mothers as statistically significant.

Statistical analysis was performed using the IBM-SPSS for Windows version 20 software (IBM Corp., Armonk, NY, USA). Descriptive statistics were calculated as numbers and percentages for qualitative data, and medians, 25th and 75th percentiles for quantitative variables. The Mann-Whitney U test was used to compare the T-FS-IS scores between those children with chewing dysfunctions and those children without chewing dysfunction. Correlation between T-FS-IS and KCPS was assessed using the non-parametric Spearman correlation coefficient. A Spearman correlation coefficient of less than 0.30 indicates a weak correlation, between 0.30 and 0.70 indicates a moderate correlation, and greater than 0.70 indicates a strong correlation (18). A p-value of less than 0.05 was interpreted as statistical significance.

Results

A total of 55 children with CP and their mothers (primary caregivers) were included in the present study. The descriptive characteristics of the children are shown in Table I.

25.5% (n=14) of the children had normal chewing function while the remaining 74.5% had some degree of difficulties with chewing. 25.5% (n=14) of the children were in level 0, 9.1% (n=5) were in level 1, 16.4% (n=9) were in level 2, 21.8% (n=12) were in level 3, and 27.3% (n=15) were in level 4 according to the KCPS classifications.

The median scores of daily activities, worry, feeding difficulties and the total score from the T-FS-IS were 3 (1.3-3.7), 2.71 (1.43-4.14), 2.16 (1.117-3.00), and 2.72 (1.38-3.61), respectively.

A moderate to strong correlation between the KCPS and daily activities, worry, feeding difficulties and the total score from the T-FS-IS was detected ($p<0.001$, $r=0.71$, $r=0.64$, $r=0.72$, $r=0.74$, respectively).

The mothers of those children with chewing dysfunction (those children with KCPS levels 1 to 4) reported more problems in the total score and all subscales of the T-FS-IS than for those children without chewing dysfunction (those children with KCPS level 0) ($p<0.01$) (Table II). The mothers' responses for each question of the T-FS-IS are shown in Table III.

Discussion

The present study shows that the chewing performance level was found to be associated with the T-FS-IS, and those mothers of children with CP who had chewing dysfunction reported more concerns relating to feeding and swallowing problems.

Table I. The descriptive characteristics of the children (n=55)

	Median	**(25-75%)**
Age (year)	3.75	2.12-5.87
WAZ	-0.68	-2.66-0.00
HAZ	-2.91	-3.90/-0.86
Feeding related characteristics		
Transition time to additional food (month)	6	6-8
Transition time to solid food (month)	8.5	8-12
Duration of mealtime (min)	27.5	14.75-30.00
Number of meals	4	3-5
Initial teething time (month)	8	7-12
Number of teeth	15	9-19
Food consistency	**Number (percentage)**	
Liquid intake	55 (100%)	
Viscous intake	55 (100%)	
Puree intake	28 (50.9%)	
Solid intake	15 (27.3%)	
Sex		
Female	23 (41.8%)	
Male	32 (58.2%)	
GMFCS		
Level 1	12 (21.8%)	
Level 2	11 (20.0%)	
Level 3	9 (16.4%)	
Level 4	8 (14.5%)	
Level 5	15 (27.3%)	
Type of cerebral palsy		
Unilateral spastic	29 (52.7%)	
Bilateral spastic	26 (47.3%)	
KCPS		
Level 0	14 (25.5%)	
Level 1	5 (9.1%)	
Level 2	9 (16.4%)	
Level 3	12 (21.8%)	
Level 4	15 (27.3%)	

WAZ: Weight-for-age Z-score, HAZ: Height-for-age Z-score

Table II. The Turkish Feeding/Swallowing Impact Survey scores of those mothers of children with and without chewing dysfunction

Turkish Feeding/Swallowing Impact Survey	**Mothers of children with chewing dysfunction**		**Mothers of children without chewing dysfunction**		**p-value**
	Median	(25-75%)	Median	(25-75%)	
Daily activities (1-5)	3,440	2.15-3.90	1	1-1	<0.01
Worry (1-5)	3.43	1.92-4.57	1	1-1.57	<0.01
Feeding difficulties (1-5)	2.50	1.66-3.37	1	1-1.17	<0.01
Total (1-5)	3.00	2.24-3.85	1	1-1.28	<0.01

Table III. The mothers' responses for each question of the T-FS-IS

Turkish Feeding/Swallowing Impact Survey	**Mothers of children with chewing dysfunction**	**Mothers of children without chewing dysfunction**	**p-value**
In the past **ONE** month, as a result of your child's feeding/swallowing problems, how often have **you** had problems **carrying out your daily activities?**	Median (25-75%)	Median (25-75%)	
To do my job, go to school, or work around the house	3 (2-5)	1 (1-1)	0.001
To get help from others because they are scared to feed or take care of my child	3 (2-4)	1 (1-1)	0.001
To leave my child because I am scared to have other people feed or take care of my child	5 (1-5)	1 (1-1)	0.002
To make plans or go out to eat with my family	5 (3-5)	1 (1-1)	0.001
To be too tired to do the things I want or need to do.	4 (2-5)	1 (1-1)	<0.01
In the past **ONE** month, as a result of your child's feeding/swallowing problems, how often have **you** had problems with **worrying?**			
My child's general health	3 (1-4)	1 (1-2)	0.15
My child does not get enough to eat or drink	4 (3-5)	1 (1-1.25)	<0.01
How others will react to my child's feeding/swallowing problems.	3 (2-3)	1 (1-1.50)	0.005
How my child breathes when feeding and whether my child will choke.	3 (2-4)	1 (1-1.50)	0.001
My child will never eat and drink like other children.	4 (3-5)	1 (1-1.25)	<0.01
Whether I am doing enough to help with my child's feeding/swallowing problems	3 (1-4)	1 (1-2)	0.010
How my child's feeding/swallowing problems affect others in my family.	2 (1-3)	1 (1-2.25)	0.286
In the past **ONE** month, as a result of your child's feeding/swallowing problems, how often have **you** had problems **feeding your child?**			
To feed my child because it takes a long time to prepare liquids and foods the "right" way.	5 (2-5)	1 (1-1)	<0.01
To feed my child because I don't know how to prepare liquids and foods.	1 (1-4)	1 (1-1)	0.028
To feed my child because others give my child liquids or foods that are not allowed.	2 (1-3)	1 (1-1)	0.011
To feed my child because I don't know how long these problems will last.	5 (3-5)	1 (1-1.25)	<0.01
To feed my child because family members or professionals have different opinions about taking care of my child's feeding/swallowing problems.	3 (1-5)	1 (1-1.25)	0.010
To feed my child because I do not get enough information about how to get my child to eat and drink like other children.	3 (1-4)	1 (1-1.25)	0.031

T-FS-IS: Turkish Version of the Feeding/Swallowing Impact Survey

This study indicates that the mothers of children with CP who had chewing dysfunction reported greater concerns in all subscales of the T-FS-IS (daily activities, worry, feeding difficulties and the total score). Children with CP may have difficulties in chewing function (19), and this may result in a restriction in the intake of the range of food textures of which these children can safely and efficiently consume (5,19). Their diet primarily consists of liquidized or pureed food textures (5,7). Therefore, we hypothesized that chewing dysfunction would increase maternal concern, and found that the mothers of children with CP who had chewing dysfunction reported more concerns relating to feeding and swallowing problems compared to those mothers of children with CP who had normal chewing function. They reported more negative perceptions of time demands on their daily activities, worry about their child's well-being, and challenges about providing care for their feeding difficulties. There may be several reasons for this. Having a child with a chronic illness already creates a burden on the family, and accompanying problems relating to the daily care of these children brings an additional burden (20,21). The possible reasons for this may be listed as (i) the need for preparation to provide appropriate food texture for those children with chewing dysfunction, (ii) increased meal preparation time, (iii) longer meal lengths, (iv) time restrictions in daily life, (v) feeling incapable of helping their child, and (vi) negative mealtime behaviors and their consequences (i.e., choking, vomiting, crying, etc.), and (vii) being unable to fully participate in social interactions. Looking at the responses on a question by question basis, the mothers reported that they were concerned about each question regarding carrying out their daily activities. They were more worried about their child' general health, and if the child was not getting enough to eat or drink, or if the child would ever be able eat or drink like other children. In terms of the problems regarding the feeding category, they were mostly concerned with the necessity of the longer time to prepare liquids and foods the "right" way, and not knowing how long these problems would last. These findings are also very important in allowing us to provide a definition for the effects of chewing dysfunction on mothers for clinicians.

There is relationship between chewing performance levels and all parameters of the T-FS-IS, which suggests that decreased chewing performance levels are related to higher problematic perceptions of the mothers, and increased chewing performance levels are related to lower problematic perceptions of the mothers. This linear correlation aligns with the comparison between those mothers of children with and without chewing dysfunction. These findings are important as chewing function has been shown to be an important function not only for the children themselves but also for their parents. In addition, these results suggest that maternal concerns should be evaluated and considered during the planning of the management of chewing dysfunction.

Study Limitations

The present study also has some limitations. The number of subjects included in the groups of children with or without chewing dysfunction was not equal. A study in which these groups are homogeneous can be planned. In addition, a healthy control group could be added for comparisons to highlight the findings. Another weak point may be the evaluation of just the mothers' responses because the primary caregivers are mothers. However, the fathers' role is also very important in families, and therefore both parents could be evaluated in future study designs. In addition, the effect of chewing training programs on parental concerns could also be assessed.

Conclusion

It is important for clinicians to know if chewing dysfunction affects parents. This study suggests that decreased chewing performance levels are associated with higher maternal concerns relating to feeding-swallowing difficulties in children with CP, and those mothers of children with chewing dysfunction reported higher concerns relating to feeding-swallowing difficulties. Therefore, special attention or additional support should be given if a child with CP has problems with solid food intake/chewing, and clinicians should also consider the quality of life of these mothers during the management of chewing dysfunctions.

Ethics

Ethics Committee Approval: This study was approved by the Non-invasive Clinical Research Ethics Committee of the Hacettepe University (approval number: GO21/206, approval date: 23.02.2021).

Informed Consent: A written informed consent form in accordance with the Declaration of Helsinki was obtained before enrollment.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.S.A., N.D., A.A.K., Design: S.S.A., N.D., A.A.K., Supervision: S.S.A., N.D., A.A.K., Data Collection and/or Processing: S.S.A., N.D., Analysis and/or Interpretation: S.S.A., N.D., A.A.K., Literature Search: S.S.A., Writing: S.S.A.

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Original Article

Adaptation and Testing of Cognitive Behavioral Therapy Resource of Turkish Version to Reduce Dental Anxiety in Children

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ABSTRACT

Aim: Dental anxiety is a common problem in pediatric dentistry and reducing it with improved communication is important. This study aimed to evaluate whether anxious children give similar answers in the dental office even though they have different cultural backgrounds and to assess the international usability of the cognitive behavioral therapy tool of the Turkish version of "Your Teeth You Are In Control" intervention including "Message to the Dentist" feedback form.

Materials and Methods: Two hundred and sixty-two children aged 5-15 years attending a faculty clinic and a private dental office were included in this study. The children were asked to complete the form to report how worried they felt and the levels of pain they experienced before and after their dental treatment on a scale of 1-10 (1=the best and 10=the worst outcome). Statistical analysis was performed with IBM SPSS V23.

Results: Most of the participants were worried about the needle, the dentist, and pain, respectively (38.2%, 34%, 28.2%). Most of the children raised their hand as a stop signal (94.7%). There was a statistically significant negative and weak correlation between age and anticipated pain, actual pain and anxiety scores (p=0.016, 0.003, 0.001 respectively).

Conclusion: The "Message to the Dentist" feedback form and cognitive behavioral therapy resource can be used in pediatric dentistry to reduce dental anxiety in its Turkish version. It was useful to understand the sources of dental anxiety in children and this can facilitate treatment by helping pediatric dentists understand how these patients feel about dental treatment procedures and, via their efforts, to improve patient care.

Keywords: Dental anxiety, children, cognitive behavioral therapy, pediatric dentistry, behavioral management

Introduction

Dental anxiety is a common problem which can be seen in both children and adults. It was stated that dental anxiety is more common in pre-school and school age children than in adolescents and it is mostly observed in the 3-18 years old age group worldwide (1). Anticipation and fear of pain in dentistry can lead to dental anxiety and avoidance of dental treatment, and many techniques have been used for pain and behavioral management in pediatric dentistry. Behavioral guidance techniques aim to foster a

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positive dental attitude so oral healthcare can be provided for infants, children, adolescents and special healthcare needs patients (2).

While dental fear, dental phobia and dental anxiety are often described as being similar, they have different meanings and should be evaluated separately (3). Dental anxiety is an emotion that may occur after a negative dental experience or it is an apprehension caused by negative dental stories acquired or heard from other people (4). Dental fear is defined as a normal emotional response to a specific real dental stimulus. Dental phobia is an intense state of dental anxiety. These lead to an avoidance of dental care (3,5). Additionally, dental anxiety can be seen at any age, especially in childhood (2,5). This issue points out the need for extra effort and time to manage individuals with dental anxiety in pediatric dentistry (4). This fear, which can be seen in various forms in children, may result in untreated dental caries and periodontal diseases in children with this avoidance (5).

Advanced techniques such as general anesthesia and sedation are available for patients with dental anxiety. However, these techniques require appropriate equipment, adequate expertise and they are high cost. Therefore, they cannot be applied at all times and in all environments and behavioral management techniques are gaining importance today. At the same time, the foundations of fear acquired in childhood are carried over into adulthood (5-8). Therefore, it is important to manage these fears correctly.

Several measurement methods have been developed to evaluate dental anxiety. Apart from measuring with scales where fear is expressed and evaluated by facial expressions or numbers, measurement methods such as drawing pictures by children have also been used (9,10). In addition to these, in order to reduce dental anxiety, various methods such as dog therapy, music, visual distraction methods, commitment therapy, cognitive behavioral therapy (CBT), relaxation, massage, acupuncture/acupressure, natural sounds and humanoid robots have been used (11-14).

CBT is a short-term psychotherapy method focused on the current problems of the patients. In CBT, the therapist applies an instructive and structured therapy method to the patient to overcome those difficulties which cannot be overcome in daily life, to solve problems, and to deal with the here and now. Furthermore, it is aimed to increase the awareness of the person, to eliminate disruptions caused by irrational thoughts in his/her life, and to replace the wrongly learned reactions with the truth (15). Relaxation exercises, breathing techniques, systematic desensitization, cognitive restructuring strategies and new behavior learning strategies are used to reduce anxiety as cognitive behavioral assessment tools (16-18). It has been reported that this technique can be preferred in many anxiety disorders as well as specific phobias such as dental anxiety or injection phobia. While dental anxiety is very common, research with CBT in children with dental anxiety is limited (6,19-21).

A CBT-based form named "Message to Dentist" (MTD) was first developed in 2017 by Porritt et al. (6). This form includes questions about anticipated pain, actual pain, anxiety levels, coping plans, stopping signals, reflections and rewards. It is used with patients both before and after dental treatment. In this form, patients are asked to rate their anxiety on a scale of one to ten (1 equals 'not scared at all') and to write down what they are worried about. The patient's expectations, wishes, how the dental examination and treatment was, and which stopping signal was preferred are asked. Moreover, patients are asked to rate their anticipated and actual pain levels on a scale of one to ten (1 is 'not painful at all'). The child is asked what they learned, what makes them feel good during the treatment, and which reward they would like next time. Porritt et al. (6) reported a significant decrease in Modified Dental Anxiety scores in children using the "Your Teeth You Are In Control" intervention with the MTD form. The "Your Teeth You Are In Control" intervention was adapted into Turkish and this was the first study to use the MTD form in Turkish children with dental anxiety. The aim of this study was to evaluate whether anxious children give similar answers in the dental office even though they have different cultural backgrounds and to assess the international usability of the MTD tool.

Materials and Methods

This study protocol was approved by the Altınbaş University Clinical Research Ethics Committee (approval no: 2021/52, date: 04.03.2021) in accordance with the World Medical Association Declaration of Helsinki before the study. Written informed consents were obtained from the participants' parents/legal guardians before the study.

Turkish Translation and Adaptation of the "MTD Form"

Firstly, the original MTD form was translated into the Turkish language by two specialist dentists and then reviewed by a lecturer from the English Department of the High School of Foreign Languages. Secondly, the English and Turkish version of the forms were sent to the researcher who created the original form and it was sent to a bilingual expert in the UK to be checked. After this stage, modifications were made in line with the recommendations given and it was applied to 30 (range=5 to 15 years) children during a two-week period. For those patients who were illiterate or had difficulty in understanding, the questions and information in the form were read to the patients by their parents or the dentist, and their answers were noted. A re-evaluation of the form was performed by two researchers and one of the developers of original form after these first and second stages. In the first version of this document, a few of the questions had problems regarding issues with Turkish socio-economic levels which could not be easily understood by the Turkish children if the document was translated word by word. For example, in the reward question, the answer part was not suitable for most Turkish children. Hence, a modification in the text was made to make it clear for the patients and some extra options were added. Additionally, most Turkish children generally sleep very late so the option of 'going to bed late' was not viewed as a reward for them. Also, golf, which was mentioned in the form, is not a common or easily accessible sport in our country and so it was removed. The children's responses were evaluated in terms of cross-cultural adaptation in this process for appropriate and understandable word usage and the final Turkish version of the form was created. The MTD form is more of a communication tool as an invention rather than a scale, although there are some questions suitable for statistical analysis and others where free text is written. The English version of this form is shown in Figure 1.

Patients who were referred to Altınbaş University Faculty of Dentistry, Department of Pediatric Dentistry and another private dental office were included in this study.

Inclusion Criteria

Children,

-Aged 5-15 years,

-Having dental anxiety but not having previous negative experiences during dental treatment in childhood or adolescence,

-Without any systemic or mental disabilities,

-Who volunteered to participate in this study and whose parental consent was obtained.

Exclusion Criteria

Children,

-Not in the age range of 5-15,

-Who did not have dental anxiety,

-Having a systemic or mental disability,

-Having previous negative experiences during dental treatment in childhood or adolescence,

-And those who did not volunteer to participate in this study or did not have parental consent for this study.

Testing of the MTD Form

This study was completely on a voluntary basis. Written informed consent was obtained from the parents of the patients and verbal consent was obtained from the patients. This form was applied in a faculty clinic or a private dental clinic to children who had not had dental treatment before and who had dental anxiety findings according to the questions. Their parents were asked to help those children who were illiterate or could not understand the questions on their own.

Preference of the stopping signal, concordance and difference between anticipated and actual pain scores, relationships in terms of age, gender, and relationships in terms of dental office or faculty clinic were examined in this study. We aimed to improve children's coping mechanisms and self-reflections with respect to dental treatment. Calibrations were performed by the examiners and the consistency of the evaluations was confirmed using a Kappa statistic. The Kappa for inter- and intra-examiner reliability was 0.94 and 0.91 respectively.

Statistical Analysis

For the sample size calculation, the G*Power (v3.1.9) program was used and when the effect size w (effect

Figure 1. English version of the MTD form
MTD: Message to Dentist

size)= 0.374 is taken, the number of samples for Power= 0.95 and α (alpha)=0.05 was determined to be minimum n=142. Data were analyzed with IBM SPSS V23. Conformity to normal distribution was evaluated by Kolmogorov-Smirnov and Shapiro-Wilk tests. The Mann-Whitney U test was used to compare the data which were not normally distributed according to the paired groups. The intra-class correlation coefficient was used to examine the concordance between the anticipated pain and the actual pain scores. Spearman's rho correlation coefficient was used to examine the relationship between data which was not normally distributed. Bonferroni correction was used as multiple comparison to compare data according to multiple choice questions. Analysis results were presented as mean ± SD for quantitative data. Categorical data as deviation and median (minimum-maximum) were presented as frequency and percentage. The significance level was taken as $p<0.05$.

Results

The form was applied to 262 children. Over two thirds (69.1%) of the participants were in the faculty clinic and 30.9% were in the private practice. 50% of the participants were female and 50% were male. The average age of the children was 8.33±2.04 years. Most of the participants were worried about needles, the dentist, and pain, respectively (38.2%, 34%, 28.2%). Other causes of dental fear were seen at lower rates, namely: dental tools, the dental room, the unit light, opening the mouth, restorative treatment, root canal treatment,

the dental unit, bleeding, water leakage into the mouth, the LED light unit, sounds, further decay of teeth, water splashing onto the face, sharp tools which may prick the cheek, nausea when taking a dental impression, the long treatment time, being tickled, the impression material which may not fit in the mouth, the impression material which may cause choking, the dentist's uniform and suction. 40.1% of the participants stated that the dental examination/treatment did not hurt as much as they expected. 29% of them did not want any reward. The most requested rewards were listed as watching a favorite program, a new toy, going to the mall, taking a courage certificate, playing a favorite game for 1 hour extra, downloading a new game, and playing with a phone, respectively (11.5%, 10.3%, 5.3%, 5%, 5%, 4.6%, 4.6%). Ninety-four point seven per cent of the children raised their hand as a stop signal. Other preferred stop signals were listed as talking, shouting, closing the mouth, raising a foot, blinking, crying, hugging their mother, hugging the dentist or pushing hands against the dentist. The best things during dental examination/treatment according to the children's answers are shown in Table I.

There was a statistically significant negative and weak correlation between age and anticipated pain, actual pain and anxiety scores (p=0.016, 0.003, 0.001 respectively). Table II represents this correlation.

The difference between the anticipated pain and actual pain was statistically different between males and females. Table III shows this difference and it is due to the sum of ranks which are greater in females.

It is shown in Table IV that as the anxiety level increases, both the anticipated and actual pain levels increase and the relationship between these two pain levels is moderate.

The children were found to be more worried in the dentist's office. Table V summarizes this, although there was no difference between the two groups (the dentist's office or the dental faculty) for actual pain, the patients felt more pain in the dental office when their anticipated pain was evaluated.

A statistically significant difference was found between the mean values of the anxiety scores according to the comments (p<0.050). Table VI contains these values and the highest mean value was obtained from the "non-cooperative patient" group (9.27), while the lowest mean value was obtained from the "very cooperative patient" group (2.19).

Table I. Frequency distribution of categorical variables

	Frequency (n)	**Percent (%)**
Best things*		
Did not hurt me, painless treatment	105	40.1
My teeth were treated	44	16.8
Nothing	19	7.3
My pain is over	16	6.1
Did not feel the injector	12	4.6
Treatment is over	10	3.8
Dentist told me everything	9	3.4
Looking at myself in the mirror	9	3.4
Treatment time was short	8	3.1
Having a break	8	3.1
Treatment was fine	5	1.9
Watching a cartoon film	5	1.9
I overcame my fear	5	1.9
My teeth are now white and more esthetic	4	1.5
Cleaning my teeth	4	1.5
Having a tooth examination	3	1.1
Receiving a reward	3	1.1
Stopping when I wanted	3	1.1
There was less nausea than I expected	2	0.8
Getting rid of my decayed tooth, cleaning my teeth	2	0.8
I was relaxed, taking a breath	2	0.8
I don't know	2	0.8
Looking at pictures	2	0.8
Getting a courage certificate	2	0.8
Extraction time was short and my dentist showed me the tooth	2	0.8
Water coming from the aerator	1	0.4
When my favorite music was playing, my fear level was reduced	1	0.4
Everything	1	0.4
*Multiple responses		

Discussion

This study aimed to investigate the levels of dental anxiety before and after dental treatment using the MTD form as part of a CBT intervention. Additionally, it aimed to understand the factors which cause dental anxiety by analyzing the content of the previous MTD research and to test whether the CBT source works in eliminating anxiety, and understanding those factors which cause dental anxiety in order to improve Health Related Quality of Life (6,21,22).

The MTD form was used with children before dental treatment to record their anticipated levels of anxiety and pain. One of the positive aspects of this study was that it allowed the children to express their own feelings and thoughts. It was also beneficial to teach child patients the stop signal, to adapt to dental treatment, and to encourage them to think positively in order to motivate themselves to deal with dental anxiety. This study is important due to the limited number of studies on children with dental anxiety related to cognitive methods (19-21,23).

In this study, the CBT method was used as a combination of some basic behavior management and communicative guidance techniques such as imagery and distraction, tell-show-do, and ask-tell-ask.

Imagery draws the child's attention away from the procedure, using imagination and storytelling. Distraction is an effective method used for pain and behavior management in pediatric dentistry and it is administered using cognitive or behavioral methods aimed at distracting attention from pain. On the cognitive side, there are methods such as counting, thinking nice things, and non-procedural talk, while on the behavioral side, methods such as videos, games and rewards can be used. The combined use of imagery and distraction has been shown to be helpful in reducing postoperative pain in children (24,25).

Tell-show-do introduces the dental hand pieces to the patient and familiarize them with the dental routine and shapes the patient's response to procedures (25).

The ask-tell-ask technique involves questioning the patient's feelings about the dental visit and any scheduled procedure (ask); explaining procedures according to the patient's cognitive level (tell); and again questioning (ask) how the patient understands and feels about the upcoming treatment (25).

CBT has a problem-focused and collaborative attitude which actively involves the patient in the process. Cognitive

Table II. Relationship between age, pain and anxiety scores

	Age	
	r	**p-value**
Anticipated pain	-0.148	**0.016**
Actual pain	-0.183	**0.003**
Pain difference	-0.006	0.925
Feeling worried	-0.202	**0.001**

r= Spearman's rho correlation coefficient

Table III. Relationship between gender, pain and anxiety scores

	Female		Male		Test statistic	p-value
	Mean ± SD	**Med (min.-max.)**	**Mean ± SD**	**Med (min.-max.)**		
Anticipated pain	4.28±3.73	2.00 (0.00-10.00)	4.08±3.85	1.00 (1.00-10.00)	U=8096.5	0.400
Actual pain	1.96±2.03	1.00 (0.00-10.00)	2.63±3.05	1.00 (1.00-10.00)	U=8064	0.299
Pain difference	2.32±3.35	0.00 (-5.00-10.00)	1.46±2.94	0.00 (-3.00-9.00)	U=7196.5	**0.010**
Feeling worried	5.53±3.77	5.00 (1.00-10.00)	5.02±3.91	5.00 (1.00-10.00)	U=7930.5	0.268

U: Mann-Whitney U test statistic
Min.-max.: Minimum-maximum, SD: Standard deviation

Table IV. Evaluation of relationship between pain scores and anxiety scores

	r	p-value
Anticipate pain	0.785	**<0.001**
Actual pain	0.474	**<0.001**
Pain difference	0.527	**<0.001**

r= Spearman's rho correlation coefficient

restructuring helps patients recognize and change false or unhelpful thoughts associated with emotional distress. It aims to eliminate fear by enabling a patient with anxiety to face the feared stimulus and situations in a planned manner (26).

In present study, the reward requests of the children were mostly related to digital content, such as watching television, playing their favorite game for an extra hour, playing with their phone, or downloading a new game, in addition to getting a new toy, going to the mall, or receiving a courage certificate. Part of this research took place during the Coronavirus disease-2019 pandemic, and due to this factor, the children may have wanted such rewards as they were mostly at home during this period and thought less of imaginative activities.

Dental injections, dentists, pain, and extractions were the things which scared the children the most. Although most of the children who participated in this study had dental anxiety, they managed to complete their treatment. The children found their dental anxiety to be relieved by having a stop signal, taking breaks during the treatment, and being provided with explanations about the instruments and the procedure. Raising the hand, which is an example of one of the stop signals given to the children before the treatment, was the most preferred and used stop signal. The response of the children to the "best things" question was often "it didn't hurt, and it was a painless treatment" as seen in Table I.

Despite the fact that no difference was found between actual pain and anticipated pain, it was thought that the reason patients felt more pain in the dental office was that the behavior guidance techniques were used more effectively by the pediatric dentists in the university pediatric dentistry clinic. Table V presents these clinical differences. It has been reported that children with severe anxiety and also in need

Table V. Relationship between dentist office/faculty clinic, pain and anxiety scores

	Dentist's office		**Dental faculty**		**Test statistic**	**p-value**
	Mean ± SD	**Med (min.-max.)**	**Mean ± SD**	**Med (min.-max.)**		
Anticipate pain	5.70±3.91	5.00 (1.00-10.00)	3.50±3.53	1.00 (0.00-10.00)	U=4669	**<0.001**
Actual pain	1.90±1.73	1.00 (1.00-10.00)	2.47 2.90	1.00 (0.00-10.00)	U=6981	0.447
Pain difference	3.80±3.85	3.00 (-3.00-9.00)	1.03±2.38	0.00 (-5.00-10.00)	U=4327.5	**<0.001**
Feeling worried	6.83±3.56	8.00 (1.00-10.00)	4.58±3.77	5.00 (1.00-10.00)	U=4901	**<0.001**

U= Mann-Whitney U test statistic
Min.-max.: Minimum-maximum, SD: Standard deviation

Table VI. Comparison of anxiety scores according to comments

	Feel worried	
	Mean ± SD	**Med (min.-max.)**
Comments*		
Non-cooperative patient	9.27±2.03a	10.00 (1.00-10.00)
Very cooperative patient	2.19±2.31b	1.00 (1.00-10.00)
I learned how to use the stop signal	6.53±3.52c	5.00 (1.00-10.00)
Cooperative patient	4.08±3.25c	4.50 (1.00-10.00)
I was relaxed, my dentist explained everything	5.06±3.76c	5.00 (1.00-10.00)
I like having treatment with breaks, step-by-step	7.05±4.08ac	10.00 (1.00-10.00)
Patient was afraid at first but then they were reassured and cooperative later	7.17±2.52ac	5.50 (5.00-10.00)
Other	5.33±3.72c	5.00 (1.00-10.00)
p-value	**<0.05**	

*Multiple responses, a-f: No difference between groups with the same letter
Bonferroni correction
Min.-max.: Minimum-maximum, SD: Standard deviation

of urgent treatment should be referred to pediatric dentists who have the ability to choose between a multitude of treatment techniques and thus employ dental treatment more appropriate to the individuality of children with dental fear (27).

Anticipated pain, actual pain, and anxiety scores decreased and had a weak correlation with increasing age, compatible with Majstorovic et al.'s (28) and Popescu et al.'s (29) studies (30). The reason for this was thought to be the increase in cognitive perception levels of the children as they grow older, which enables them to control their reactions. It has been stated that dental anxiety in different age groups is related to different perspectives of dentistry and explained by the shift of dental anxiety from basic primary stimuli to more complicated causes (31,32).

Gender differences in dental fear in children are a widely researched topic. Some studies did not find a significant difference between boys and girls, but most of them reported that girls have more dental anxiety than boys (5,33-35). In the current study, girls had more dental anxiety than boys (Table III).

The results of this study indicated that as the anxiety levels increased, the actual and anticipated pain levels also increased, as summarized in Table IV. In another study, it was reported that less fear was felt in situations where pain was experienced personally, except for patients with high dental anxiety. This situation was considered to be triggered by the objectively distorted perception of the expected toothache before dental treatment in children with high stress and anxiety levels (35). This finding was compatible with the present study.

In another study using Internet-based CBT, it was reported that this method was feasible and effective for anxious children and adolescents in pediatric dentistry (36).

In a systematic review, it was stated that CBT reduces dental anxiety more effectively than various behavioral management techniques, but more studies are needed in children due to the low quality of this evidence (37).

Study Limitations

The study was carried out in a single city and with a small population. However, despite this seeming limitation, Istanbul is a multicultural city of 20 million people who have emigrated from all of Turkey and a tool which works for Istanbul can be applied all over Turkey. In addition, the fact that children do not have any difficulties in understanding and answering the questions and helping the dentist with their answers can be taken as an indication that this method is suitable for Turkish children.

In further studies, new information can be obtained with a larger sample group with more children, and this method's effectiveness may be compared with other techniques.

Conclusion

It is important for pediatric dentists to be aware of new behavior management approaches and to use these techniques to improve their patients' experiences of dental care.

The MTD form and CBT resource can be used in pediatric dentistry to reduce dental anxiety of children in Turkey. It was useful to show how children's anticipated fear and pain levels reduced following treatment and to identify the specific causes of their concern. This method of understanding and correcting the source of dental anxiety in children can facilitate treatment by helping pediatric dentists understand how these patients feel about dental treatment procedures and to guide their efforts in order to improve patient care.

The Turkish version of the MTD form has been used successfully similar to the original version. As in cases of its successful use in other languages or cultures, this version can also be considered an international supportive method for dentists in the treatment management of patients with anxiety.

Ethics

Ethics Committee Approval: This study protocol was reviewed and approved by the Altınbaş University Clinical Research Ethics Committee (approval number: 2021/52, date: 04.03.2021) in accordance with the World Medical Association Declaration of Helsinki before the study.

Informed Consent: Written informed consents were obtained from the participants' parent/legal guardian and the study protocol was approved by the institute's committee on human research.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Design: A.T.G., Z.M., Data Collection and/or Processing: A.T.G., E.A.T., B.A., G.E., Analysis and/or Interpretation:

A.T.G., B.Ö., Z.M., Critical Review and Editing: Z.M., B.Ö., Writing: A.T.G., E.A.T.

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Original Article

The Effect of Kangaroo Care and Breastfeeding on Reducing the Pain due to Hepatitis B Vaccine Injection in Newborn Infants: A Comparative Analysis

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ABSTRACT

Aim: This study was conducted to compare the effects of breastfeeding (BF) and kangaroo mother care in newborns on the level of pain and physiological changes due to an injection of the hepatitis B vaccine.

Materials and Methods: This study was designed as a comparative experimental study. The sample of this study consisted of a total of 70 infants, including 35 in the Kangaroo group and 35 in the BF group, who were followed up in the postnatal ward at Zeynep Kamil Training and Research Hospital between August 2016 and February 2017 and who also met the sample criteria. The pain levels, duration of crying, heart rates (HR) and oxygen saturation (SpO_2) of the newborn infants were compared before and after a hepatitis B vaccine injection.

Results: It was determined that there was no statistically significant difference between the infants in the BF and kangaroo mother care groups in terms of their pain scores (Z=0.949; p=0.343), SpO_2 levels (Z=1.032; p=0.302), HR (Z=0.206; p=0.837) and duration of crying (Z=0.135; p=0.892). Following the vaccination, the HR and pain scores of the infants in the BF gruop increased by less and they had a shorter duration of crying.

Conclusion: According to these results, BF infants is effective in reducing the pain induced by invasive interventions as this is easily applicable, takes little time, encourages breast milk and strengthens the mother-infant attachment.

Keywords: Hepatitis B, pain, breastfeeding, kangaroo mother care, infant

Introduction

The Taxonomy Committee of the International Association for the Study of Pain defines pain as an unpleasant biochemical or emotional condition or behavior which arises from a certain area of the body, depends or does not depend on tissue damage, is affected by an individual's previous experiences and aims to detract from an undesired condition (1). A common opinion which was believed until the 1980s was that newborns did not perceive pain adequately due to their underdeveloped nervous systems due to their incomplete myelination. In those years, the high risk of side effects from and addiction to analgesics, the thought that the experience of pain does not affect the newborn and ethical contradictions prevented the examination of pain

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and its effects in the newborn (2). Studies have shown that breast milk and skin-to-skin contact have proven analgesic effects, and breast milk has positive effects on a newborn's heart rate (HR), oxygen saturation (SpO_2) and crying time after a painful intervention (3).

Vaccinations that are frequently applied to healthy children cause feelings of pain in these children.

Consequently, both pharmacological and non-pharmacological methods are used to reduce these feelings of pain (4). Non-pharmacological methods include breast milk, changing position, kangaroo care and touching, massage, sucrose application, giving a pacifier, and playing music (2,5,6). Although all these interventions have been shown to provide a significant difference when applied alone, the number of the studies comparing these interventions is very limited. In the present study, it was thought that comparing effective interventions in reducing pain, such as "kangaroo mother care" (KMC) and "breastfeeding" (BF), would be indicative in reducing pain of infants who cannot be breastfed.

In the present study, we aimed to investigate a comparison of the physiological effects of BF and kangaroo care in newborns on the level of pain induced by the injection of the hepatitis B vaccine.

Materials and Methods

Sample

The sample of the study consisted of a total of 70 infants, including 35 in the KMC group and 35 in the BF group, who were followed up in the postnatal ward at Zeynep Kamil Maternity and Children Training and Research Hospital between August 2016 and February 2017 and who met the sample criteria.

The inclusion criteria for this study were as follows: newborns whose parents participated voluntarily in this study and who were born full-term by vaginal delivery, had a body weight of 2,500-4,000 grams, had 1-minute and 5-minute Apgar scores of >7, had a postnatal age within the first 24 hours, were examined by a physician and accepted to be healthy, and had no skin lesions. The exclusion criteria for this study were as follows: those who were born in the 36+6 weeks of gestation or before according to their mothers' last menstrual date, were older than 24 hours or had health problems.

As a result of the Power analysis (G*Power 3.1.9.2) which was conducted for the experimental study based on a similar previous study (4), it was found that when taking D as 1.97 in the evaluation conducted based on the post-procedure pain scores of the infants, the sample size determined for Power=0.80, b=0.20, and a=0.05 was specified to be a total of 12 individuals (minimum 6 individuals for each group). In a standard experimental study, it is recommended to include 30 individuals in each group in order to conduct the study with 80% power (7). As a consequence, when considering its applicability in statistical tests, the sample group consisted of a total of 70 infants comprising 35 in the experimental group and 35 in the control group by taking possible case losses into consideration in order for the data to have strong reliability.

Randomization

This study was conducted using a randomization method (drawing lots). In the lots method, 35 red cards and 35 yellow cards were put into a black bag. Before the infant was assigned to the study group, the service nurse was asked to draw a card from this bag. Red cards represented the BF group, while yellow cards represented the kangaroo care group.

Data Collection Tools

The following tools and forms were used to collect the data of the study.

- Data Collection Form,
- Neonatal/Infant Pain Scale (NIPS),
- Pulse Oximeter,
- Chronometer.

Data Collection Form

In order to record the data of the study, the data collection form was prepared by the researchers in accordance with the literature. The data collection form consisted of two sections. The First Section consisted of 13 questions about the infant's date of birth, postnatal age, week of gestation, delivery method, gender, Apgar score, medical diagnosis, birth weight, height, head circumference and feeding style, whether or not the infant was stable in their general condition and whether the infant had any skin damage or not. The Second Section involved NIPS evaluation criteria used to evaluate the infant's pain score.

Neonatal/Infant Pain Scale

NIPS was developed by Lawrence et al. (8) and its Turkish validity and reliability study was conducted by Akdovan and Yıldırım (9). It is a scale developed specifically for newborn infants. It consists of a total of 6 criteria; facial

expression, crying, breathing patterns, arm movements, leg movements, and state of arousal. There are 2 scorings (0-1) in all categories except for crying, which has 3 scorings (0-1-2). The total score of the scale varies between 0 and 7. A high score signifies a higher intensity of pain.

Pulse Oximeter

A calibrated Nellcor pulse oximeter was used to measure the SpO_2 and HR of both groups before and after the vaccination.

Chronometer

The infants' duration of crying was evaluated with the chronometer of an Iphone 6s. The chronometer was started at the moment when the infant started crying and stopped at the moment when the infant stopped crying.

Procedure

The infants to whom kangaroo care would be applied were undressed in a way that only their diapers were left, which provided skin-to-skin contact with their mothers.

Conversely, those infants in the BF group were undressed only on one leg to allow for the injection, held on their mothers' lap and the BF was started.

Before the vaccination, a pulse oximeter probe was attached on the infants in both the KMC and BF groups and their pain scores, SpO_2 and HR values were recorded.

The vaccine injection was performed three minutes after the KMC or BF interventions were initiated (4). When the infant started crying during the vaccination, the researcher started the chronometer and when the crying stopped, the chronometer was stopped and the duration of crying was recorded. As soon as the injector was removed from the infant's leg, HR and SpO_2 were recorded with the help of the pulse oximeter in both the BF and kangaroo care groups and then the NIPS was evaluated.

Data Assessment

The results obtained from this study were evaluated using IBM SPSS Statistics 22 (IBM SPSS, Turkey) program for statistical analyses. The suitability of certain parameters for the normal distribution was evaluated with the Shapiro Wilks test. In the assessment of the data of this study, along with descriptive statistical methods (mean, standard deviation, frequency), Student's t-test for normally distributed ones and Mann-Whitney U test for non-normally distributed ones were used to compare the quantitative data between two groups. The chi-square test, Yates's Correction for Continuity, and Fisher's Exact chi-square tests were used to compare qualitative data. Significance was evaluated at a level of $p<0.05$.

Ethical and Legal Aspects of the Study

In order to conduct this study, ethics committee approval (IRB: 205) was received from Zeynep Kamil Maternity and Children Training and Research Hospital and institutional permission was obtained. For the NIPS used to evaluate pain in this study, written permission was obtained from Yıldırım who authored the Turkish validity and reliability study from the Children's Hospital of Eastern Ontario Research Institute via e-mail. Before conducting this study, the mothers of all the infants were informed about the study and their written permission was obtained via an informed consent form.

Results

The descriptive characteristics of the infants included in this study are presented in Table I. The infants in this study were all healthy and only breastfed. When comparing the descriptive characteristics of the infants according to the groups, it was determined that there was a statistically significant difference between the groups in terms of the week of gestation (Z=-2,662, p=0.008). When comparing the infants birth weight (Z=-0.311, p=0.756), height (Z=-0.012, p=0.990) and head circumference (Z=-0.061, p=0.952), there was no statistically significant difference between the groups (Table II).

There was no significant difference in terms of SpO_2 (Z=-1,895, p=0.058) and HR (Z=-0.723, p=0.470) between the groups. It was observed that there was a significant decrease in the SpO_2 of the infants in both groups and an increase in their HR values after the vaccination (Table III). When the groups were compared in terms of the difference in the decrease of SpO_2, it was determined that there was no significant difference between the infants in the KMC (-4.09±5.22) and BF (-4.49±6.08) groups (Z=-0.212, p=0.832). Similarly, it was observed that there was an increase of 16.17±11.43/min in the HR in the KMC group and an increase of 15.14±14.01/min in the BF group. There was no statistically significant difference between the groups (Z=-1,681, p=0.093) (Table III).

When comparing the groups in terms of the duration of crying, it was observed that there was no statistically significant difference (Z=-0.135, p=0.892). When comparing the groups in terms of NIPS score, it was also seen that there was no statistically significant difference between them (Z=-0.949, p=0.343) (Table IV).

Discussion

Non-pharmacological methods used to reduce pain in newborns include kangaroo care and BF. It has been determined that BF (10) and kangaroo care are effective at reducing pain (11).

Sajedi et al.'s (12) study examining the effect of kangaroo care on physiological parameters during intramuscular injections in newborns, determined that SpO_2 which was 97.2 before the injection decreased to 97.1 after the injection in the kangaroo care group. The reason for the stability of SpO_2 was associated with the vitamin K administration, which was different from the present study. This suggests that the hepatitis B vaccine causes a greater sense of pain than vitamin K injection.

Efe and Ozer (13) reported on the effects of BF on pain experienced during a vaccination stating that the HR of infants which was 138.85±35.89/min before the vaccination increased to 153.36±29.60/min after the vaccination, which

Table I. Distribution of the descriptive characteristics of the infants (n=70)

Characteristics		**Min.-Max.**	**Mean ± SD**
Gestation week (w)		37-42	39.04±1.41
Age (hour)		3-24	14.07±6.13
1st min APGAR		7-9	7.26±0.50
5th min APGAR		8-10	9.77±0.46
Birth weight (g)		2,500-4,000	3.297.14±381.09
Length (cm)		45-56	49.76±2.01
Head circumference (cm)		29-38	33.74±1.54
Characteristics		**n**	**%**
Sex	Girl	39	55.7
	Boy	31	44.3
Medical diagnosis	Healthy	70	100.0
Feeding choice	Breast milk	70	100.0
General health status	Quiet	70	100.0
Skin damage	Absent	70	100.0

SD: Standard deviation, Min.: Minimum, Max.: Maximum

Table II. Comparing the descriptive characteristics of the infants according to the groups (n=70)

Characteristics		**Kangaroo (n=35)**	**Breastfeeding (n=35)**	**Z**	**p-value**
		(Median)	**(Median)**		
Age (hour)		12.43±6.40 (12)	15.71±5.46 (16)	-2,327	0.020*
Gestation week (w)		39.56±1.22 (40)	38.48±1.42 (38)	-2,662	0.008**
1st min APGAR		7.40±0.55 (7)	7.11±0.40 (7)	-2,735	0.006**
5th min APGAR		9.66±0.48 (10)	9.89±0.40 (10)	-2,499	0.012*
Birth Weight (g)		3.310.29±387.03 (3,350)	3.284.00±380.24 (3,300)	-0.311	0.756
Height (cm)		49.86±1.93 (50)	49.66±2.11 (50)	-0.012	0.990
Head circumference (cm)		33.83±1.50 (34)	33.66±1.59 (34)	-0.061	0.952
		n (%)	**n (%)**	**χ2**	**p-value**
Sex	Girl	21 (60)	18 (51.4)	0.232	0.630
	Boy	14 (40)	17 (48.6)		

Z: Mann-Whitney U test; χ^2: Continuity (Yates) chi-square test
*p<0.05; **p<0.01

was similar to the present study. Efe and Ozer (13) reported that SpO_2 which was 96.64±2.93% before the intervention decreased to 95.97±3.08% after the intervention. In contrast to the present study, this smaller decrease in SpO_2 was associated with the fact that the age (2-4 month-old infants) of their sample group was higher than in the present study.

In the study by Fallah et al. (14) which compared the effects of kangaroo care, BF and swaddling on infants vaccinated with Bacillus, Calmette-Guerin (BCG), the infants were breastfed for two minutes before the vaccination and one minute during and after the vaccination, whereas the kangaroo care was applied ten minutes before the intervention and for one minute during and after the intervention. In the BF group, the duration of crying was found to be 26.61 seconds just as in the present study. However, it was observed that the duration of crying was two times longer in the kangaroo care group (45.12 seconds) than in the study group of the present study. In the study by Fallah et al. (14), the reason for the duration of crying being two times longer than the present study despite a longer period of kangaroo care was associated with the BCG vaccination.

Kashaninia et al. (15) evaluated the behavioral reactions of 100 healthy newborns to intramuscular injection and found that pain scores were lower in the kangaroo care group than in the control group to whom no kangaroo care was applied. At the same time, the duration of crying was found to be 14.55 seconds in the kangaroo care group and 24.61 seconds in the control group. The difference in

Table III. Distribution and comparison of SpO_2 and HR levels of infants before and after the vaccination (n=70)

Characteristics		**Kangaroo (n=35)**	**Breastfeeding (n=35)**	**[1]Z**	**p-value**
		(Median)	**(Median)**		
O_2 saturation	Before vaccine	96.37±2.59 (97)	97.46±2.24 (98)	-1,895	0.058
	After vaccine	92.29±4.81 (94)	92.97±6.39 (95)	-1,032	0.302
	Difference	-4.09±5.22 (-3)	-4.49±6.08 (-3)	-0.212	0.832
	[2]Z	-4,446	-3,635		
	p	0.001**	0.001**		
HR	Before vaccine	129.20±14.93 (130)	132.69±16.62 (129)	-0.723	0.470
	After vaccine	145.37±14.58 (146)	147.83±18.82 (144)	-0.206	0.837
	Difference	16.17±11.43 (18)	15.14±14.01 (13)	-1,681	0.093
	[2]Z	-4,670	-4,919		
	p	0.001**	0.001**		

[1]Z: Mann-Whitney U test, **p<0.01
[2]Wilcoxon Signed Rank test
HR: Heart rates

Table IV. Comparing the distribution of pain scores and the duration of crying of the infants before-after the vaccination (n=70)

Characteristics		**Kangaroo (n=35)**	**Breastfeeding (n=35)**		
		(Median)	**(Median)**	**[1]Z**	**p-value**
Duration of crying (seconds)	Before vaccine	0.00±0.00 (0)	0.00±0.00 (0)	0.001	1.000
	After vaccine	22.14±17.37 (18)	18.6±8.54 (18)	-0.135	0.892
	[2]Z	-5,013	-5,090		
	p	0.001**	0.001**		
NIPS score	Before vaccine	0.00±0.00 (0)	0.00±0.00 (0)	0.001	1.000
	After vaccine	6.46±1.27 (7)	6.29±1.36 (7)	-0.949	0.343
	[2]Z	-5,508	-5,373		
	p	0.001**	0.001**		

[1]Z: Mann-Whitney U test, **p<0.01
[2]Wilcoxon Signed Rank test

the data acquired from that study regarding the duration of crying in comparison to the results of the present study may be associated with the fact that vitamin K was administered intramuscularly in the study by Kashaninia et al. (15).

Kostandy et al. (16) suggested that skin-to-skin contact decreased the feeling of pain caused by the hepatitis B vaccine. They applied kangaroo care to newborns 10-15 minutes before the intervention, and found the duration of crying after the vaccination to be 16 seconds. The reason for the duration of crying being shorter than in the present study may be associated with the kangaroo care being applied to the newborns for 15 minutes before the intervention which is 12 minutes longer than in the present study.

Efe and Savaşer (10) examined the effects of BF and oral sucrose on pain caused by peripheral venous blood-letting in 102 newborns. They found that the duration of crying was 28.62±33.71 seconds in the BF group. The reason for the duration of crying being longer in those newborns in the BF group than for those in the present study may be associated with the difference of the intervention. Additionally, Efe and Savaşer (10) determined that the HR value which was 147.8±14.16/min before the intervention increased to 153.2±18.4/min after the intervention in those infants to whom sucrose was applied and the HR value which was 142.9±13.7/min before the intervention increased to 153.2±27/min after the intervention in those infants in the BF group and that there was no difference between them. In the study by Efe and Savaşer (10), HR increased by 10.3/min in the BF group before and after the application and by 15.14/min in the present study. It was thought that the difference of 4.84 /min between them may be associated with the differences between the interventions applied as the venous blood-letting procedure caused a longer sense of pain than the hepatitis B vaccine.

In their study examining the effects of various interventions applied to newborns on pain and the duration of crying, Yilmaz and Arikan (17) divided 120 newborns to whom heel lance would be applied into four groups, namely; breast milk, sucrose, pacifier and control groups. Two mL of breast milk was given to the breastmilk group via an injector two minutes before the procedure. The HR of the breast milk group increased from 132.60/min to 156.87/min after the intervention, which is similar to result of the present study. The reason for the higher HR rate values after the intervention compared to the present study was associated with the fact that the intervention was applied during BF in the present study, whereas in the study by Yilmaz and Arikan (17), breast milk was given via an injector before the intervention and also the heel lance application is a procedure lasting for a longer period.

In the present study, the pain score of the BF group to whom the hepatitis B vaccine was applied was found to be 6.29±1.36 over 7 points; whereas, in the study by Koç and Gözen (5), the pain score of the reflexology group was found to be 5.47±2.11 over 10 points. The pain scales used in the two studies are different but when compared, the pain score was found to be higher in the present study. The fact that the infants were older (6 months) and reflexology was applied as a method of reducing pain in the study by Koç and Gözen (5) was thought to have resulted in this difference as the infants in the present study were newborns and more sensitive to pain.

Study Limitations

Before the study, pain assessment was planned to be evaluated by a nurse who was blinded to the research and who would watch video camera recordings of the infants during the vaccine injection. However, it was considered that it would not be ethical to take video footage during BF and KMC and so the assessments were made by the researcher. Therefore, the limitation of this study was the lack of observers who were blinded to the research.

Conclusion

It was determined that even though there was no significant difference between the SpO_2 and HR levels between the groups before and after the vaccination, the HR of the BF group increased by less than KMC group after the vaccination.

The NIPS pain score was found to be lower in the BF group after the vaccination but this difference was not statistically different between the groups. Those infants in the BF group had a shorter duration of crying than those in the KMC group although this was not statistically significant. According to these results, it can be seen that BF is effective in order to reduce pain in infants induced by invasive interventions. Additionally, BF is easily applicable, takes little time, encourages breast milk and strengthens the mother-infant attachment.

Acknowledgements

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Ethics

Ethics Committee Approval: In order to conduct this study, ethics committee approval (IRB: 205) was received from Zeynep Kamil Maternity and Children Training and Research Hospital and institutional permission was obtained.

Informed Consent: Before conducting this study, the mothers of all the infants were informed about the study and their written permission was obtained via an informed consent form.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: T.K.T., Design: T.K.T., D.G., Data Collection and/or Processing: T.K.T., Literature Search: T.K.T., Writing: T.K.T., D.G.

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

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Original Article

Evaluation of Allergen Sensitization in Patients with Allergic Rhinitis and/or Asthma in Tekirdağ

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ABSTRACT

Aim: Allergic rhinitis (AR) and asthma are the most prevalent allergic diseases, and environmental allergens are important factors in the pathogenesis and the exacerbation of these diseases. Although there are many studies investigating aeroallergen sensitivities in different regions of our country, this study aimed to identify the aeroallergen sensitization in the Tekirdağ province in the part of Turkey in Europe, namely Thrace, where it is important to know aeroallergen sensitivities.

Materials and Methods: Four hundred and sixty children with asthma and AR who were followed up and had at least one aeroallergen sensitivity in a skin prick test (SPT) were retrospectively evaluated. All patients had undergone a SPT using the standard extracts, including house dust mites, molds, animal dander, pollens, and latex.

Results: The mean age of the patients was 10.2±3.4 (5-18) years, 57.6% of them were male. The diagnoses of the patients were AR in 57.8%, asthma in 22.6% and both in 19.6%. 42.6% (n=196) of the patients were sensitized to more than one allergen. The most common aeroallergens in SPT were house dust mites (63%), grass-rye mix (26.5%), grass mix (26.1%), molds (19.8%), cat epithelium (11.3%), cockroach (8.5%), weed mix (7%), olive tree (7%), dog (5.7%), cupressus (4.3%), tree pollen mix (3.5%), poplar (1.5%), mugwort (1.3%), and latex (0.4%). Although the cockroach, pet, olive tree and multiple allergen sensitivities were more frequent among male children ($p<0.05$), there was no association between gender and sensitivity to the other allergens. There was no difference between the aeroallergen distributions of the patients according to diagnoses ($p>0.05$). House dust mites were the most common allergens throughout all seasons.

Conclusion: The results of this study will be important in guiding elimination measures against the triggering allergens which are important for the treatment and the course of the disease of the those patients with asthma and/or AR in this region.

Keywords: Aeroallergen sensitivity, children, Tekirdağ, allergic rhinitis, asthma

Introduction

Allergic rhinitis (AR) is one of the leading causes of morbidity worldwide, and its prevalence is gradually increasing. AR is also frequently associated with asthma and is a risk factor. AR and asthma affect the quality of life and the school and work performances of the patients and they lead to frequent hospital visits (1).

AR is the most common atopic disease and it affects more than 500 million people worldwide (2). It is characterized by symptoms such as runny and itchy nose, sneezing and nasal obstruction. It has been reported to affect 10-40% of children and adults in the United States and other industrialized countries (3-5).

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Asthma is characterized by bronchial hyper-reactivity and chronic inflammation, causing reversible obstructions of the airways due to an interaction between hereditary and environmental factors (6). Three hundred million people worldwide are diagnosed with asthma (7). Asthma, commonly seen in childhood, is one of the critical reasons for morbidity. A variety of environmental factors such as viral infections, aeroallergens such as house dust mites (HDMs) or pollens, and tobacco exposure can result in asthma exacerbation (8).

Allergen sensitization refers to allergen-specific immunoglobulin E (IgE) production and it is assessed by using a skin prick test (SPT) or by measuring allergen specific IgE levels. Although allergen sensitization does not cause symptoms in some individuals, some may experience allergic symptoms. Atopy is an important risk factor for asthma, AR, and other allergic diseases. The elimination of triggering allergens is important for the optimal management of allergic diseases in order to reduce symptoms and control these diseases, and it constitutes the first-line therapy (9).

The SPT is a quick, affordable, and effective method with high sensitivity and specificity to detect aeroallergen sensitivity in IgE-mediated allergic diseases such as asthma and AR. The most commonly seen aeroallergens are HDMs, grasses, trees, weed pollens, animal dander, and molds (10).

Tekirdağ is a coastal city situated on the northwest coast of the Marmara Sea in the Marmara region of Turkey, consisting of different regions presenting a variety of climate characteristics. It has coasts on both the Marmara and the Black Sea and it has a sub-humid climate.

The most important feature of this research is that Tekirdağ, the province where the study was conducted, is located in the part of Turkey in Europe, namely Thrace. Since this region has different climatic characteristics, the distribution of allergens may be variant. Therefore, studies are required in order to identify allergen sensitivities in those children with asthma and AR in Tekirdağ, a city located in the Marmara region of Turkey.

The purpose of this study was to determine the distribution of aeroallergen sensitivities in those children with AR or/and asthma in Tekirdağ by using a SPT.

Materials and Methods

Patients aged between 5 and 18 years with asthma and AR were followed up between September 2018 and February 2020 in the Pediatric Allergy and Immunology Outpatient Clinic and they were confirmed to have at least one aeroallergen sensitivity. SPTs were included in this study. Their demographic characteristics, total IgE levels, eosinophil counts and percentages in peripheral blood, and aeroallergen sensitivities in SPTs were investigated retrospectively. Those patients with a chronic disease other than an allergic disease were excluded from this study.

The diagnosis and management of asthma were made in line with the Global Initiative for Asthma guidelines (8). AR was diagnosed based on the AR and Their Impacts on Asthma guidelines (1).

This study was approved by the Tekirdağ Namık Kemal University Faculty of Medicine, Non-Invasive Clinical Research Ethics Committe (date: 25/03/2020, no: 2020.66.03.16).

Skin Prick Test

Medicines which may affect SPT results were discontinued at an appropriate time before the test. The SPTs of all of the patients were performed on the forearms and evaluated 15-20 minutes after the application by measuring the wheal diameter (11). Positive control (histamine 10 mg/mL), negative control (0.9% NaCl), and standardized commercial allergen solutions were used in the SPTs (®ALK-Abelló, Copenhagen, Denmark). The allergens applied in SPTs were: HDMs (Dermatophagoides farinae, Dermatophagoides pteronyssinus); molds (Alternaria alternata, Aspergillus fumigatus, Cladosporium herberatum); grass pollen mixture; weed pollen mixture; 9 tree pollen mixture; grass-rye mixture; animal dander (cat, dog); cockroach (Blattella germanica); cupressus; Engl. Plantain; mugwort; olive; poplar; nettle; and latex allergen extracts.

A wheal diameter ≥3 mm larger than the negative control was considered as allergen sensitivity (11).

Mite sensitivity was defined as a sensitivity to at least one of the HDMs. Animal dander and epithelium sensitivity was defined as a sensitivity to at least one of the cat or dog epitheliums. Mold sensitivity was defined as a positive reaction to at least one of the molds in the SPT. Tree pollen sensitivity was defined as a sensitivity to at least one of the tree pollens.

Statistical Analysis

Statistical analyses were performed using the SPSS Version 22.0 statistical software package (IBM SPSS Statistics Chicago, Ill). Descriptive statistics were expressed as mean, standard deviation, median, minimum and maximum values, frequencies, and percentages. A chi-square test was used in the analysis of the categorical data. Whether the distribution of each variable in the dataset

fitted the normal distribution was tested, and variables that were not normally distributed were evaluated by non-parametric tests (Kruskal-Wallis test and Mann-Whitney U test). P<0.05 was considered statistically significant.

Results

Four hundred and sixty children aged between 5 and 18 years with asthma and/or AR who were followed up and had at least one aeroallergen sensitivity in SPT were retrospectively evaluated. The aeroallergen sensitivities with SPT were 63% for HDMs, 26.5% for grass-rye mix, 26.1% for grass mix, 19.8% for molds, 11.3% for cat epithelium, 8.5% for cockroach, 7% for weed mix, 7% for olive tree, 5.7% for dog, 4.3% for cupressus, 3.5% for tree pollen mix, 1.5% for poplar, 1.3% for mugwort, and 0.4% for latex (Figure 1).

The mean age of the patients was 10.2±3.4 (5-18) years, and 57.6% were male. The diagnoses of the patients were AR in 57.8%, asthma in 22.6%, and both AR and asthma in 19.6%. 16.7% (n=31) of the patients had concomitant atopic dermatitis. 42.6% (n=196) of the patients were sensitive to more than one allergen. The clinical and laboratory findings of the patients are summarized in Table I.

There was no difference between the diagnoses according to age, presence of atopic dermatitis, laboratory findings, or multiple allergen sensitivity (Table II).

When aeroallergen sensitivities were assessed according to diagnoses, there was no difference between the aeroallergen distributions of the patients (p>0.05). The percentages of aeroallergen sensitivities according to diagnoses are shown in Figure 2.

There was no difference between the genders according to age, the presence of the accompanying atopic dermatitis, total IgE levels, eosinophil count and the percentages (p>0.05, data not shown). The cockroach sensitivity (p=0.004), the pet sensitivity (p=0.006), and the olive tree sensitivity (p=0.01) were more frequent among male children. However, there was no relationship between the genders in terms of the sensitivity to the other allergens (data not shown). In this study, 52.4% (n=243) of the patients had more than 4% of eosinophils, and there was no difference between the genders (p=0.07). 51.7% (n=238) of the patients had a total IgE level higher than the age-appropriate reference range.

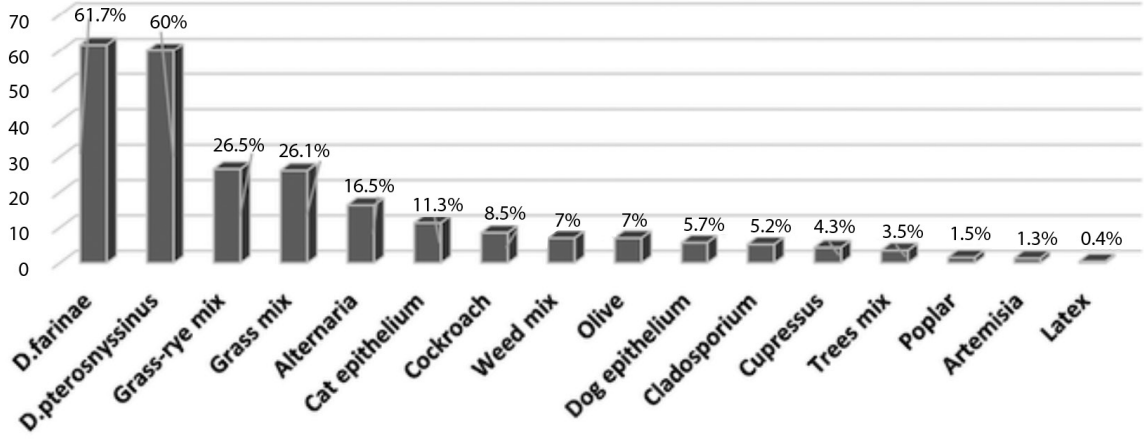

Figure 1. Allergens sensitization in skin prick test

Table I. Clinical and laboratory characteristics of the patients	
Age	10.2±3.4 (5-18) years
Gender, n (%)	n=195 (42.4) female, n=265 (57.6) male
Distribution of diagnoses, n (%)	n=266 (57.8) allergic rhinitis, n=104 (22.6) asthma, n=90 (19.6) allergic rhinitis and asthma
Multiple allergen sensitivity, n (%)	n=196 (42.6)
Total IgE (median) kU/L	166 (4-2,582)
Eosinophil count (/mm^3)	368±270 (77-1,450)
Eosinophil percentage (%)	4.5±3.5 (0.5-28)

The presence of the accompanying atopic dermatitis was not related to gender, aeroallergen sensitivities, or laboratory parameters (p>0.05, data not shown).

Aeroallergen sensitivities in the SPT were evaluated according to the seasons. There was no seasonal difference between the distribution of the aeroallergen sensitivities, and HDMs were the most common allergens throughout all of the seasons (Figure 3).

Multiple allergen sensitivity was more frequent among males (65.3%, n=128) than females (34.7%, n=63) (p=0.004). The distribution of the diagnoses and the presence of the multiple allergen sensitivity were not associated (p=0.54).

Discussion

Identifying the triggering allergens and taking elimination measures as early as possible is important in asthma and AR courses. Several studies have shown that the aeroallergen distributions vary significantly from country to country and region to region according to factors such as climate, humidity, and temperature (11-13). Therefore, it is necessary to know the aeroallergen sensitivities of each region. Although there are many studies investigating aeroallergen sensitivities in different regions and provinces of our country, this study's difference and importance is that it was conducted in Tekirdağ province in the Thrace region where aeroallergen sensitivities were in need of investigation.

This study evaluated the aeroallergen sensitivities via SPTs of those children with AR and/or asthma in Tekirdağ, Turkey. The most common aeroallergens were seen to be HDMs, grass-rye mix, grass mix, and molds.

The prevalence of AR has gradually increased, especially in early childhood (14,15). It was reported that 38% of patients with AR have asthma (16). In this study, 76.4% (n=356) of the patients had AR, and 25.2% (n=90) of patients had asthma.

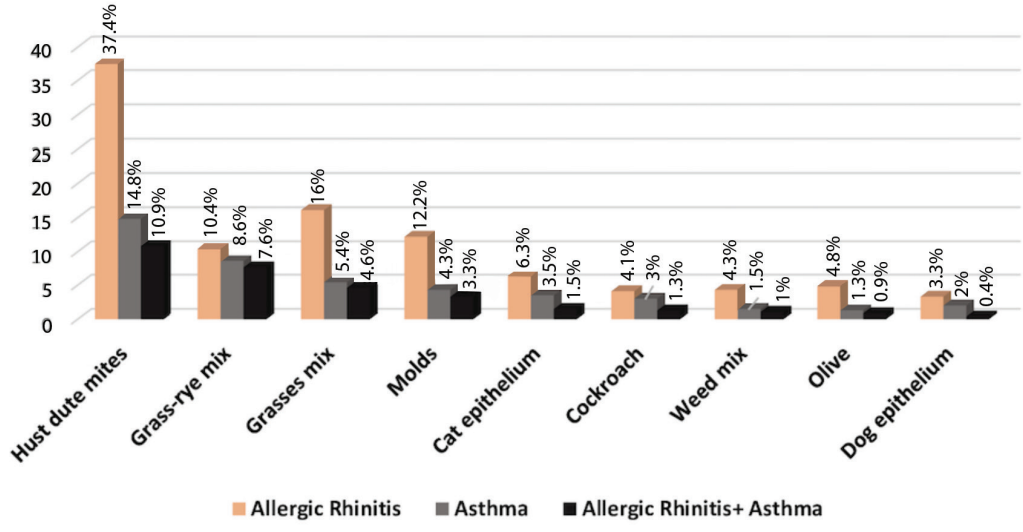

Figure 2. Distribution of allergens sensitization according to diagnoses

Table II. Patient characteristics and laboratory findings according to diagnoses

	Allergic rhinitis n=266	Asthma n=104	Allergic rhinitis and asthma n=90	p-value
Age (years)	10.3±3.3 (5-18)	9.9±3.6 (5-17)	10.5±3.5 (5-17)	0.8
Gender (male)	57.5%	65.5%	53.3%	0.66
Total IgE (median) (kU/l)	176 (4-2,980)	201 (5-2,500)	148 (10-2,500)	0.4
Eosinophil count (/mm^3)	382±281 (77-1470)	373±273 (60-1800)	300 250 (30-1,450)	0.52
Eosinophil percentage (%)	5.2± 3.8 (0.5-28)	5±3.1 (0.5-17.3)	4.9±3 (0.6-14.2)	0.6
Presence of atopic dermatitis	5.5%	1.1%	0.7%	0.6
Multiple allergen sensitivity	45.1% (n=120) yes	42.3% (n=44) yes	35.6% (n=32) yes	0.12

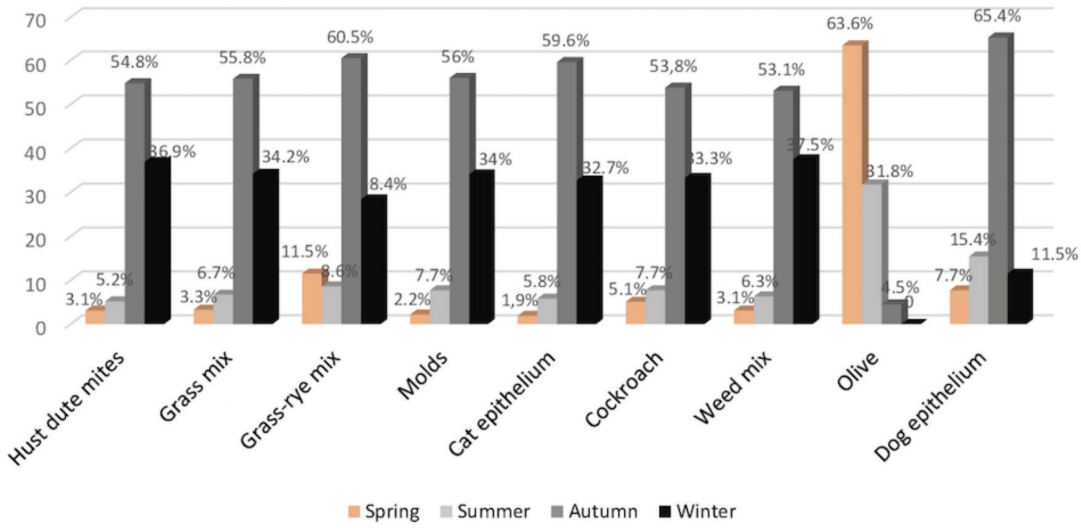

Figure 3. Distribution of allergens sensitization according to seasons

It has been reported that atopy is more common in males (17). In our study, in according with the literature, 57.6% of the patients with a sensitivity via SPT were male, and 42.4% were female.

Inhaled allergens can originate from indoors or outdoors. While HDMs, animal allergens, cockroach allergens, and many molds are indoor allergens, pollens, some other molds, and animal allergens are outdoor allergens, which are affected by the weather and season (18). HDMs are strongly associated with the pathogenesis of AR and asthma, and delays in diagnosis can result in a decrease in the effectiveness of the treatment (19). HDMs are the most common allergens in patients with asthma in central Anatolia, with a prevalence of 63.3%, according to the study by Cengizlier and Misirlioglu (20).

Mites are mostly found in hot and humid environments and optimally live between 25-30 degrees and at 75-80% humidity. In our country, HDMs were founded to be the most common allergens in those studies conducted in warm and humid cities such as Istanbul (96.7% Der. Pteronyssinus, 89.3% Der. Farinae) and Samsun (97%) (21,22). Similar to other studies, the most common allergen sensitivity was HDM (63%) in this study. Leung et al. (23) reported that D. Pteronyssinus and D. Farinae were closely associated with sensitivity. In our study, 89% of those patients sensitive to D. Farinae were also sensitive to D. Pteronyssinus. Regarding the multiple aeroallergen sensitivity of those patients sensitive to house mites, 22.7% (n=66) had pollen mix sensitivity, and 14.4% (n=42) had mold sensitivity.

Tekirdağ is a coastal city situated on the northwest coast of the Marmara Sea in the Marmara region of Turkey, which consists of different regions presenting a variety of climate characteristics. It has coasts on both the Marmara Sea and the Black Sea and has a sub-humid climate. In the only study to date conducted in Tekirdağ by Nalbantoğlu et al. (24) reported that the most common allergen was the HDM (59%) in children with AR.

Pollens are one of the most common causes of airway allergies. Sensitivity to grass, grass-mix, tree, and weed pollens are frequently detected, and pollens with clinical significance vary from region to region. Grass pollens are the most important allergen group in our country and many other European countries. In our cities with hot and dry climates, such as Malatya (48.9%) and Ankara (23.6%), grass pollen was reported to be the most frequent cause of allergen sensitivity (25,26). Tekirdağ has a Mediterranean climate characterized by the hot summers and warm winters. In our study, grass-rye mix (26.5%) and grass mix (26.1%) were found to be the most common pollens, and grass pollen was the second most common allergen causing sensitivity in SPT after the HDMs.

Ay et al. (26) reported that 73 out of 236 children with asthma aged between the 6 and 18 years had coexisting AR and these children had more pollen and grass mix sensitivity than those children with asthma only (total pollen 16.5%, 39.7%; grass pollen 3.7%, 8.7%). There was no difference in aeroallergen sensitivities in our study according to diagnoses.

Fungus spores are also one of the important indoor allergens. In studies conducted in the cities of Turkey, mold sensitivity rates were high, being 51.2% in Sakarya, 43.4% in Antalya, and 30% in Ankara (27-29). In our study, mold (19.6%) was the third most frequent allergen, and its frequency was similar to that of Mersin (19.4%) (30). In places where pets are frequently found, associated pet allergies through sensitization gain importance. The frequency of pet allergies is higher in European countries, in parallel with their economic development. In our country, animal dander allergy is 28.7% in the Eastern Black Sea region, 16% in Izmir, and 6% in Sakarya (27,31,32). In our study, the pet sensitivity ratio was 13.9%, cat sensitivity was 11.3%, and dog sensitivity was 5.7%.

Cockroaches are important environmental allergens, and cockroach exposure occurs most commonly in the urban regions where there is a higher cockroach density, gloomy rooms, kitchens, and bathrooms, especially in the temperatures between 20-25 °C and relative humidity of 60-75%. Cockroaches are found more in places where the living conditions and socio-economic status are poor. In the study by Celmeli et al. (33), cockroach sensitivity was found to be 25.4% and was associated with AR and asthma in Turkish children. In different studies, cockroach allergy was as high as 30% in Malatya and as low as 16.9% and 2.5% in Antalya and Ankara (25,26,28). The cockroach allergy was relatively low, at 8.5% in our study, and this was thought to be due to the socio-economic and cultural development of the Tekirdağ region.

Multiple allergen sensitivity was detected in our study in 42.6% of the patients. This result was similar to a study conducted in Mersin that found the rate of poly-sensitization to be 39.5% (30). Although the aeroallergen sensitivities, total IgE levels, eosinophil counts, and percentages were not associated with the presence of poly-sensitization in our study; poly-sensitized patients had higher total IgE levels in the study of Arıkoğlu et al. (30), but the presence of poly-sensitization was not related to age, gender, total IgE level or eosinophil count in the study by Topal et al. (25).

In a study conducted in the USA to determine the eosinophil counts and serum IgE levels of children with asthma, eosinophil percentages were more than 4% in 48.3% of the male children and 35.1% of the female children (34). In our study, 52.4% (n=243) of the patients had an eosinophil percentage of more than 4%, but there was no difference according to gender.

High IgE levels can be seen in patients with atopic diseases (35). However, the level of total IgE alone is insufficient to confirm allergic diseases (36). In our study, age-appropriate Total IgE elevation was found in only 52.7% of the patients, according to the reference values defined in the literature (37).

When the SPT results were evaluated according to the seasons, in our study, similar to a study in the Antalya region (28), HDMs were the most common allergen in all seasons. This result shows the necessity of being careful about HDMs throughout the year. However, in a study in Malatya province, it was reported that sensitivity to HDMs was most common in winter and sensitivity to grass-cereals pollen mixture most frequently in summer (25).

Conclusion

In conclusion, aeroallergen sensitivities play an important role in childhood AR and asthma. Our study identified the environmental allergen sensitivities and common allergens in the SPTs of those children with AR and/or asthma in Tekirdağ. According to SPT results, the most common sensitivity was to HDMs. Cockroach, pet, and olive sensitivities were more common among male children. Aeroallergen sensitivity in SPT were not associated with the diagnoses. We think that this study will be a guide to help in taking appropriate elimination measures which are important in managing airway allergies.

Ethics

Ethics Committee Approval: This retrospective analysis was approved by the Local Ethics Committee of Tekirdağ Namık Kemal University (date: 25.03.2020, approval no: 2020.66.03.16).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: N.C.G., C.T., N.S., Design: N.C.G., C.T., E.T., A.N., B.N., Supervision: N.C.G., B.N., N.S., Materials: N.C.G., C.T., E.T., A.N., Data Collection and/or Processing: N.C.G., C.T., E.T., Ş.G.K., A.N., Analysis and/or Interpretation: N.C.G., C.T., B.N., Ş.G.K., N.S.

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Original Article

The Significance of Immunoglobulins in Cystic Fibrosis: Normal or High?

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ABSTRACT

Aim: Cystic fibrosis (CF) is characterized by local and chronic inflammation accompanied by increased neutrophil and macrophage counts, high elastase levels, and inflammatory cytokines due to impaired haemostasis. Changes in immunoglobulin (Ig) levels may occur due to recurrent chronic infections and may be associated with the deterioration of respiratory functions. In this study, we aimed to evaluate the interaction of high Ig levels with respiratory functions and chronic infections in CF.

Materials and Methods: The diagnosis of the patients CF was made in accordance with the "National CF Diagnosis and Treatment Guidelines". The socio-demographic characteristics, Ig values, and the pulmonary function tests were evaluated according to age group.

Results: A total of 107 patients were included in this study. The patients' median age was 65 (6-200) months. It was found that those patients with high IgG (p=0.01) and IgA (p<0.001) values had more moderate-to-severe respiratory function than those with normal values. Also, there was no statistically significant difference when the patients were compared for *P. aeruginosa* colonization using IgG levels (p=0.51), IgA levels (p=0.16) and IgM levels (p=0.34).

Conclusion: Elevated IgG and IgA levels in patients with CF may be an indirect indicator of deterioration in pulmonary function tests. There was no significant difference in IgG, IgA, and IgM levels for *P. aeruginosa* colonization. We recommend that the results of our study be supported by cohort studies.

Keywords: Cystic fibrosis, immunoglobulins, chronic inflammation, respiratory functions

Introduction

The cystic fibrosis (CF) disease is caused by a defect in the CF transmembrane regulator gene, which produces a protein called CF transmembrane conductance regulator (CFTR) (1,2).

CF is characterized by local and chronic inflammation accompanied by increased neutrophil and macrophage counts, high elastase, and inflammatory cytokines due to impaired haemostasis. Changes in immunoglobulin (Ig) levels may occur due to recurrent chronic infections and inflammation in the respiratory tract (3-6). Mutations which cause disruptions in CFTR function lead to abnormal mucus viscosity and disruptions in mucociliary clearance, allowing permanent airway colonization, especially with pathogenic bacteria. Chronic colonization with *Pseudomonas aeruginosa* and *Staphylococcus aureus* usually occurs in CF. An association between chronic colonization with *P. aeruginosa* and elevated IgG levels and subtypes has been demonstrated (3,7,8). Higher IgG

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and IgA levels have been associated with worse clinical outcomes and increased impairment of lung function in CF patients (4,9,10). A study conducted on child and adult CF patients found positive correlations between IgG and CRP, and negative correlations between CT scores and spirometry. The use of IgG as a marker for CF disease activity is supported by the available literature (11). Interestingly, hypogammaglobulinemia has been reported to be associated with less severe lung disease and therefore, better prognosis (4,5,9). Although many mechanisms have been blamed for the pathogenesis of polyclonal Ig activity in CF, the real mechanism is not clear. IgG levels may reflect a hyperimmune state with no apparent effect on recurrent infections, possibly causing damage to the airways (11). Given this context, this study aimed to evaluate the interaction of high Ig levels with respiratory functions and chronic infections in CF.

Materials and Methods

Patients who were diagnosed with CF between 6 months and 18 years old and followed up by the Department of Paediatric Chest Diseases between December 2012 and December 2021 were evaluated. Approval was obtained from the Dicle University Faculty of Medicine Non-Invasive Research Ethics Committee (number: 507, date: 15.12.2021). The diagnosis of CF was evaluated according to the "National CF Diagnosis and Treatment Guidelines": Clinical findings of CF disease or sibling history with CF or neonatal screening test positivity and at least one of the following: showing 2 mutations of CF or measurement of nasal potential difference compatible with CF or two different sweat test results performed on the same day are ≥60 mEq/Lt (12,13).

The socio-demographic characteristics routinely checked, single Ig values, and laboratory parameters from the previous three months were evaluated. Levels of IgG, IgA, IgM, and IgE were expressed as being within the normal or above (hyper) two standard deviations from the age-corrected mean. The results were compared to the age-related national normal population data (14). Routine C-reactive protein (CRP) and haemogram values taken at the same time as Igs were evaluated.

Body weight, height measurements, and pulmonary function tests (PFT) recorded simultaneously with the last laboratory tests of the patients were evaluated according to age groups. Nutritional status was evaluated by calculating weight for height (BGA) percentiles for those patients in the first two years of life, and body mass index (BMI) percentiles for those aged between three to 18 years. The nutritional status of the patients whose BGAs and BMIs were below the 10^{th} percentile were considered inadequate (13).

The patients were evaluated during clinical stability. Those patients with a background of intervention with gamma globulin, cancer immunosuppression therapy, transplant or those with acute lung infection, or any immunodeficiency such as humoral and/or cellular immunodeficiency were excluded from the Ig analysis (15).

The patients' forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), FEV_1/FVC, and maximum expiratory flow at 50% of vital capacity (FEF_{25-75}) were assessed. The severity of the lung disease was evaluated according to the FEV_1 percentages. Cases with a FEV_1 of 81% and above were accepted as normal, between 51% and 80% as mild, between 31% and 50% as moderate, and less than 30% as severe (16). PFTs within the last three months were evaluated. The Ig levels and PFT were evaluated during clinical stability.

Those patients with bronchiectasis on chest tomography taken within the last six months, and *P. aeruginosa* and *S. aureus* colonization in their sputum cultures over three consecutive months in the last six months were included this study.

Statistical Analysis

SPSS-18 was used to conduct statistical analyses for this study. Visual (histogram and probability graphs) and analytical (Kolmogorov-Smirnov/Shapiro-Wilk tests) methods were employed to verify whether the variables conformed to the normal distribution. Descriptive statistics are given, including the median for numerical non-normally distributed variables and the mean for normally distributed variables. The chi-square test (χ^2) was used to compare categorical variables. Correlation analyses were calculated using the Pearson test.

Results

The clinical characteristics and laboratory parameters of the patients are shown in Table I. A total of 107 patients were included in this study. Of these, 61 patients were male (57%) and their median age was 65 (6-200) months. Fourty-eight patients were diagnosed via new-born screening (44.9%). Genetic testing was carried out on 102 patients. Genetic mutation was detected in 82 patients (76.7%). Homozygous 3130delA/3130delA was the most common mutation. Chronic *P. aeruginosa* colonization was seen in 17 patients (15.8%). Median CRP was 0.07 (IQR=0.24).

The evaluation of IgG, IgA, and IgM levels according to the age of the patients is shown in Table II. Ig values were found to be normal in most of the patients. Eighty-three of the patients were below 10 years and 9 (10.8%) of them had high IgG.

The comparison between different parameters and IgG levels is shown in Table III. Sixty-four of the patients could perform PFTs. Three patients (5.6%) had normal to mild FEV_1 and high IgG. Also, three patients (30%) had moderate to severe FEV_1 and high IgG. This was statistically different (p=0.01). Forty patients were below 10 years of age and could perform a PFT. Four out of 40 patients (10%) had high IgG. Two of the other 24 patients (8%) who were above 10 years of age had high IgG. This was not statistically different (p=0.76). Nutritional status was inadequate in 25 patients. Five out of 25 patients (20%) had high IgG. Also, 6 out of 82 patients (7.6%) with a normal nutritional status had high IgG. This was not statistically different (p=0.08).

The interactions between the parameters and IgA levels are shown in Table IV. There was a significant difference between the groups in terms of FEV_1 (p<0.001). It was determined that those patients with high IgA levels had more moderate-to-severe respiratory function.

The interactions between the parameters and IgM levels are shown in Table V. There was no statistically significant difference between the groups in terms of FEV_1 (p=0.2), *P. aeruginosa* colonization (p=0.34), nutritional status (p=0.73), or age (below or above 10 years old) (p=0.18).

The relationships between Ig levels and CRP, absolute neutrophil, and eosinophil count are shown in Table VI. There was no significant correlation between increases in Ig levels and these laboratory parameters.

Discussion

Ig levels may be elevated because of aging, reflecting a deterioration in lung function and chronic lung infections in patients with CF (4,5,17). Therefore, monitoring IgG and IgA levels in CF patients may be useful for this purpose. In this study, the interaction of Ig changes with both *P. aeruginosa* colonization and PFT were evaluated in patients with CF.

Various mutations were found in 75% of the patients in the study that was conducted by Onay et al. (18). The most common mutation was the delta F508 mutation (18.8%), and the second most common mutation was 1677delTA (7.3%). Erdem et al. (19) found various mutations in 75% of their patients, and the delta F508 homozygous mutation

Table I. Clinical characteristics and laboratory parameters of the patients

Age, median (min.-max.), months		65 (6-200)
Age at diagnosis (months), median (min.-max.)		4 (0-244)
Follow-up durations (months), n (IQR)*		98 (51)
Gender, male/female (%)		57/43
Consanguineous marriage, n (%)		58 (54.2)
Newborn screening diagnosis, n (%)		48 (44.9)
Genetic mutation detected, n (%)		82 (76.7)
Most common mutation	Homozygous 3130delA/3130delA, n (%)	8 (7.5)
	Homozygous delta F508/delta F508, n (%)	7 (6.5)
Median FEV_1** (IQR)		89 (33)
Chronic *P. aeruginosa* colonization n (%)		17 (15.8)
Chronic *S. aureus* colonization n (%)		7 (6.5)
Median number of polymorphonuclear neutrophils (IQR)/mm^3		4000 (3580)
Median CRP, mg/dL (IQR)**		0.07 (0.24)
Malabsorption***, n (%)		18 (30.7)
The rate of bronchiectasis, n (%)		24 (22.4)
Age of first bronchiectasis occurrence, mean ± Standard deviation		102±39.4
Nutritional status****, inadequate, n (%)		25 (23.4)

*IQR: Interquartile range
**Sixty-four patients were able to perform pulmonary function test
*** Stool elastase >200 microgram/day was considered as malabsorption.
****Nutritional status was evaluated by calculating weight for height percentiles for patients in the first two years of age, and body mass index percentiles for patients aged between three to 18 years
min.-max.: Minimum-maximum, FEV_1: Forced expiratory volume in 1 second, CRP: C-reactive protein

(12.5%) was found most frequently. In our study, genetic mutation was detected in 82% of the patients. The most common mutations were homozygous 3130delA/3130delA (7.5%) and homozygous delta F508/delta F508 (6.5%). Due to the heterogeneous structure of the Turkish population, different regional genotypic results have been reported in studies. Due to these different genotypic features, genotype results in patients with CF in our country may vary locally, but in general, the homozygous delta F508/delta F508 mutations are common.

Moss's (3) study found that patients with CF had higher IgG levels than the control groups. Hypergammaglobulinemia was detected in 34.2% of the cases (3). During follow-up in a cohort study, Proesmans et al. (17) also found that the rate of hypergammaglobulinemia had increased from 16% to 25% over the years. Garside et al. (4) found hypergammaglobulinemia in 7.8% of CF patients below 18 years of age. In addition, this rate was found to be 1.2% in patients below the age of 10 and 15.5% in those above the age of 10, and this difference was significant (4). In the study by Matthews et al. (5), the rate of hypergammaglobulinemia in the paediatric population was found to be 6.5% for those below the age of 10, and 24.7% for those above the age of 10, and this was found to be statistically significant. The rate of hypergammaglobulinemia was found to be greater in those studies conducted on adults. Hassan et al. (20) found this rate to be 69% between the ages of 17 and 49 years and Pressler et al. (21) found it to be 32% between the ages of one and 36 years. We found that 11 (10.3%) of our patients had hypergammaglobulinemia and our results were very similar to other studies conducted with children. However, in terms of hypergammaglobulinemia values, no statistically significant difference was found between those patients below or above 10 years of age who were able to perform PFTs. In fact, the median age of our patients was 65 months. We know that chronic infections and inflammation are relatively rare at this age (22). It was stated by Ortega-López et al. (10) that hypergammaglobulinemia was the result of chronic airway inflammation due to chronic infection. Also, adult patients were not included in our study. The

Table II. Number and rates of cases with normal or high immunoglobulin levels by age groups

Ig values	Categorical age	Normal* n (%)	High* n (%)
IgG	Below 10 years, n=83	74 (89.2)	9 (10.8)
	Between 10-18 years, n=24	22 (91.7)	2 (8.3)
IgA	Below 10 years, n=83	74 (89.2)	9 (10.8)
	Between 10-18 years, n=24	19 (79.2)	5 (20.8)
IgM	Below 10 years, n=83	79 (95.2)	4 (4.8)
	Between 10-18 years, n=24	21 (87.5)	3 (12.5)
IgE	0-18 years, n=107	104 (97.2)	3 (2.8)

*Levels of IgG, IgM, IgA were assessed as being normal or above (hyper) the standard deviations from the age-corrected mean
Ig: Immunoglobulin

Table III. Interaction between the parameters and IgG levels

Parameters		Normal IgG n (%)	High IgG n (%)	p-value
FEV_1*	Normal to mild, n=54	51 (94.4)	(5.6)	0.01
	Moderate to severe, n=10	7 (70)	3 (30)	
Age*	Below 10 years old and those who could do pulmonary function test, n=40	36 (90)	4 (10)	0.76
	Above 10 years old and those who could do pulmonary function test, n=24	22 (91.7)	2 (8.3)	
Nutritional status, inadequate	Yes, n=25	20 (80)	5 (20)	0.08
	No, n=82	76 (92.7)	6 (7.3)	
Malabsorption**	Yes, n=18	15 (83.3)	3 (16.7)	0.32
	No, n=89	81 (91)	8 (9)	
P. aeruginosa colonization	Yes, n=17	16 (94.1)	1 (5.9)	0.51
	No, n=90	80 (88.9)	10 (11.1)	
S. aureus colonization	Yes, n=7	5 (71.4)	2 (28.6)	0.1
	No, n=100	91 (91)	9 (9)	
Bronchiectasis***	Yes, n=24	19 (79.1)	5 (20.9)	-
	No, n=7	7 (100)	0 (0)	

*Only 64 patients were able to perform pulmonary function tests.
**Stool elastase >200 microgram/day was considered as malabsorption.
***Computed tomography was performed in 26 of the patients in the normal IgG group with suspected bronchiectasis, and in 5 of the patients in the high IgG group
FEV_1: Forced expiratory volume in 1 second, Ig: Immunoglobulin

incidence of hypergammaglobulinemia is less common in children than in adults. This has been attributed to less *P. aeruginosa* colonization and the treatment of inflammation with antibiotics (4,5).

Further, it has been shown that CF patients with high IgG levels had more severe clinical outcomes and worse lung functions compared to those with normal levels (4,9). In our study, we found that lung functions were affected more severely in patients with hypergammaglobulinemia. This supports the results observed during the literature review. In addition, when evaluated in terms of *P. aeruginosa* colonization, no significant difference was found between the groups with or without hypergammaglobulinemia. Bronchiectasis was detected in all patients with hypergammaglobulinemia. It was difficult to evaluate the difference between colonization and the age groups based on our study. Cohort studies would be able to provide more accurate information. Our study supports previous findings that an increase in IgG may be an indicator of lung function damage (9,23).

It has been stated by Aanaes et al. (24) that IgA elevation is significant when *P. aeruginosa* is present in respiratory

Table IV. Interaction between the parameters and IgA levels

		Normal IgA n (%)	**High IgA n (%)**	**p-value**
FEV_1*	Normal to mild, n= 54	47 (87.1)	7 (12.9)	<0.001
	Moderate to severe, n=10	3 (30)	7 (70)	
Nutritional status, inadequate	Yes, n=25	20 (80)	5 (20)	0.24
	No, n=82	73 (89)	9 (11)	
P. aeruginosa colonization	Yes, n=17	13 (76.5)	4 (23.5)	0.16
	No, n=90	80 (88.9)	10 (11.1)	
Malabsorption**	Yes, n=18	14 (77.8)	4 (22.2)	0.2
	No, n=89	79 (88.8)	10 (11.2)	
S. aureus colonization	Yes, n=7	6 (85.7)	1 (14.3)	-
	No, n=100	87 (87)	13 (13)	
Age	Below 10 years, n=83	74 (89.2)	9 (10.8)	0.21
	Above 10 years, n=24	19 (79.2)	5 (20.8)	

*Only 64 patients were able to perform pulmonary function tests.
**Stool elastase >200 microgram/day was considered as malabsorption
FEV_1: Forced expiratory volume in 1 second, Ig: Immunoglobulin

Table V. Interaction between the parameters and IgM levels

		Normal IgM n (%)	**High IgM n (%)**	**p-value**
FEV_1*	Normal to mild, n=53	50 (94.3)	3 (5.7)	0.2
	Moderate to severe, n=11	10 (90.9)	1 (9.1)	
Nutritional status, inadequate	Yes, n=25	23 (92)	2 (8)	0.73
	No, n=82	77 (93.9)	5 (6.1)	
Malabsorption**	Yes, n=18	16 (88.9)	2 (11.1)	0.39
	No, n=89	84 (94.4)	5 (5.6)	
P. aeruginosa colonization	Yes, n=17	15 (88.2)	2 (11.8)	0.34
	No, n=90	85 (94.4)	5 (5.6)	
S. aureus colonization	Yes, n=7	6 (85.7)	1 (14.3)	-
	No, n=100	94 (94)	6 (6)	
Age	Below 10 years, n=83	79 (95.2)	4 (4.8)	0.18
	Above 10 years, n=24	21 (87.5)	3 (12.5)	

*Only 64 patients were able to perform pulmonary function tests.
**Stool elastase >200 microgram/day was considered as malabsorption
FEV_1: Forced expiratory volume in 1 second, Ig: Immunoglobulin

tract secretions and is an indicator of *P. aeruginosa* infection. In another study, it was found that the group with high IgA levels had a higher rate of *P. aeruginosa* colonization (71.4%) than the group with normal IgA (23.5%). Also, it was found that those patients with high IgA levels had a higher rate of severe FEV_1 classification (71.4%) than the group with normal IgA (8.8%) (10). Our study was not a cohort study. The median age of the patients was 65 months, and they were part of the age group with lesser bronchiectasis and chronic colonization. In our study, no significant difference was found in terms of *P. aeruginosa* colonization and IgA levels. Interestingly, it was observed that IgA elevation could be accompanied by a moderate to severe deterioration in PFT.

In a study evaluating 53 patients with CF, high levels of IgM were found in seven patients (13%). A similar rate of severe involvement in FEV_1 was found between the high IgM group (18.8%) and the normal group (28.6%). High IgM levels were detected in one patient below 10 years of age (14.3%) and in four patients above 10 years (57.1%). *P. aeruginosa* colonization (>three months) was detected in six patients with high IgM (18.8%) and in seven patients with normal values (100%). In addition, bronchiectasis was detected in 10 patients with high IgM (29.4%) and in six patients with normal IgM (85.7%). Malnutrition was observed in 11 patients with normal IgM (34.4%) and in three patients with high IgM (42.8%), all of whom were below 18 years of age. The significance of these differences was not mentioned (10). In our study, no significant association was found between FEV_1 level, age, nutritional status, *P. aeruginosa* colonization, and IgM elevation. Further research is needed to explain the importance of IgM elevation in CF. It is difficult to comment on this subject with the current literature knowledge.

Gur et al. (25) found a relationship between IgG and CRP levels in adult patients with CF. CRP is a marker for inflammation which increases during pulmonary exacerbations and decreases after antibiotic therapy (26). Even in stable patients, higher CRP levels were associated with worse FEV_1 values (27). Higher IgG and CRP levels were found to be associated with disease severity (26,28). We did not find a significant relationship between high IgG levels and CRP or neutrophil counts in our patients during clinical stability.

Table VI. The relationship between Ig levels and CRP, absolute neutrophil, and eosinophil count

		C-reactive protein (mg/dL)	Absolute neutrophil count	Absolute eosinophil count
IgG	r	0.02	-0.19	0.15
	p	0.86	0.87	0.2
IgA	r	0.18	0.12	-0.19
	p	0.1	0.17	0.08
IgM	r	0.18	0.18	-0.1
	p	0.1	0.09	0.33

Ig: Immunoglobulin, CRP: C-reactive protein

Study Limitations

The main limitations of our study are the relatively small number of patients and its single-centre nature. The significance of some differences could provide a more accurate assessment in larger patient groups. Additionally, when studies are limited to children, ensuring homogeneity among groups becomes difficult. We believe that cohort studies will yield more accurate results. Since our study is prospective, it is difficult to evaluate the significance between acute *P. aeruginosa* infections and Ig levels. The effect of low Ig levels on the airways was not evaluated in our study. We were also unable to assess changes in IgG levels over time, due to our study's nature. We did not have the subtypes of IgG in our data, and therefore, could not evaluate correlations between subtypes of IgG and disease severity. Levels of other inflammatory markers, such as cytokines, were not available.

Conclusion

Elevated IgG levels in patients with CF may be an indirect indicator of deterioration in PFT. There was no significant difference between *P. aeruginosa* colonization and IgA and IgG elevation. We surmise that an increase in IgA may be an indicator of a deterioration in PFT. We recommend that the results of our study be supported by larger population and cohort studies.

Ethics

Ethics Committee Approval: Approval was obtained from the Dicle University Faculty of Medicine Non-Invasive Research Ethics Committee (number: 507, date: 15.12.2021).

Informed Consent: Informed consents were not required because the study was conducted retrospectively.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: V.Ş., A.K., Design: V.Ş., A.K., Data Collection and/or Processing: S.S., Writing: A.K., M.T.

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Original Article

The Relationship Between Internet Addiction, Cyberbullying and Parental Attitudes

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ABSTRACT

Aim: This descriptive study was conducted in order to determine the relationship between internet addiction, cyberbullying, cyber victimization and parental attitudes towards them.

Materials and Methods: The sample consisted of 550 students attending the ninth grade who volunteered to participate in this study. Consent from the ethical committee, institute and the parents were obtained for this study. Data were collected using the Student Individual Information form, Young's Internet Addiction Test-short form, Cyberbullying scale, Cyber Victimization scale and Parental Attitudes Scale.

Results: It was determined that 47.1% of the students had a computer or a tablet and 99.5% of them had a smartphone; 44.9% of the students used a computer once a week, and 57.4% used a smartphone to watch videos or films or to follow social media. There was a positive relationship between Young's Internet Addiction test and the Cyberbullying scale while there was a negative relationship between internet addiction and cyber victimization ($p<0.05$).

Conclusion: According to these results, educational programs for adolescents and their parents should be developed related to internet use in adolescents and the risks of addiction, and cyberbullying.

Keywords: Adolescent, cyberbullying, cyber victimization, internet addiction, parental attitudes

Introduction

The internet has provided a new communication medium and is used worldwide (1-3). However, the unprecedented increase in internet use has compounded certain problems caused by the overuse of the internet. The most significant problem, defined as overuse of the internet, is internet addiction (4,5). It has been reported that the overall prevalence of internet addiction ranges from 2.6% to 10.9% in Western and Northern Europe, and the Middle East, respectively (6). Adolescents' internet addiction in other studies were found to be; 1.98% in Norway, 20.8% in Taiwan, 6.44% in China, 10.7% in South Korea, 8.1% in the USA, 1.4% in females in Finland and 1.75% in males, 5.4% in Italy and 1.2% in Turkey (7,8).

Adolescents' (aged between 12 and 18) need for social interaction results in newly established relationships with their peers. Nowadays, this need may be met through social media sites (9). Face-to-face contact of adolescents

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has decreased due to widespread access to digital forms of social interaction through social media thanks to internet technologies (10). As the literature shows, internet addiction may have negative effects on physical, psychosocial and cognitive fields due to overuse of the internet (11,12). A problem caused by widespread internet use is the concept of bullying which is taken into the virtual dimension (13,14). One study on this subject showed that violent online games cause psychosocial problems such as aggressiveness (15). The act of bullying online is defined as "cyberbullying" (13).

Cyberbullying, as a major youth problem worldwide, usually refers to repeated, intentional aggression that can transpire at all hours through digital channels (e.g., smartphones or emails) (14,16-18). Cyberbullying prevalence ranges from 15% to 41% among U.S. adolescents (19). In Cook's (1) study (2021), it was found that 47.7% of parents with children aged 6-10 years, 56.4% of parents with children aged 11-13 years and 59.9% of parents with children aged 14-18 years reported that their children were bullied. In Lee and Shin's (20) study, 34% of the respondent students were involved in cyberbullying, either as bullies (6.3%), as victims (14.6%), or as both bullies and victims (13.1%). Many studies found that, as time on the internet increased, so did cyberbullying and victimization levels. There was a strong, linear relationship among internet addiction, cyberbullying, and victimization (21-23). It was stated that cyberbullying increased in parallel with cyber victimization and that problematic internet use was an important determinant in cyberbullying attitude (24,25). Evidence has revealed that those adolescents exposed to cyberbullying have a higher probability of problems related to aggression and disregarding of rules (26) and they can show similar behaviors (27). It is stated that an adolescent exposed to cyber victimization may show cyberbullying-related behaviors with a sense of anger and revenge and these behaviors can be periodically repeated (28).

However, previous research has primarily focused on the relations between personal factors and cyberbullying perpetration, and the potential relations between family factors and cyberbullying perpetration have received scant attention (14,29). Adolescents who use the internet for long periods of time do not receive enough social support from their families and lack communication within the family. Adolescents who have strong relationships with their family and friends spend less time on the internet. Internet addiction has a negative effect on inter-family communication as well as social life (18). Aktürk and Çiçek (30) (2017) reported that those students who did not have a good relationship with their families tended to use the internet as a means to distance themselves from their families; as a result, it was concluded that the level of internet addiction was higher among such students. It is thought that the satisfaction that adolescents can get from their relationships with their families is very important in terms of problematic internet use.

School health services have an important place in providing preventive health practices and behaviors in schools that have the largest role in terms of reaching children. Bullying and internet addiction are important problems that concern school health professionals (such as physicians, nurses, psychologists, social workers) (21). School nurses have significant responsibilities in providing school-age children with preventive health care and the acquisition of healthy lifestyle behaviors.

The frequency of internet use, the degree of internet addiction and cyberbullying of children and adolescents and the parental attitude regarding this subject should be assessed and recognized.

The present study aimed to determine the relationship between ninth grade students' internet addiction, cyberbullying, cyber victimization and parental attitudes.

The study sought to answer these questions:

- "*Is there any relationship between the internet usage characteristics and internet addiction and cyberbullying and victimization in adolescents?*"

- "*To what extent do internet usage characteristics and internet addiction effect cyberbullying and victimization?*"

- "*Is there any relationship between internet addiction, cyberbullying, cyber victimization and parental attitude?*"

Materials and Methods

Participants

This descriptive study was carried out with high school students in a city in Turkey. The study was conducted in the 2017- 2018 academic year. The study population was 2,571 ninth grade students (male: 1,410, female: 1,161) who lived in the city.

The study sample, which was determined using the known population sampling method, were 334 students for a 95% confidence interval. Four different high school types with in city (science, Anatolian, religious vocational and vocational/technical high schools) were assigned a number, evenly distributed, and selected using a random numbers table in order to reach the desired sample size. The

sample size was obtained from four high schools. This study included 550 students.

Criteria for Inclusion in the Study

Students who used a computer, tablet, or smartphone, who volunteered for the study and whose parents gave informed consent were included in this study. Adolescents use the internet more than other age groups because they are more interested in technology and have not reached psychological maturity yet and constitute a risk group for internet addiction (22,23).

Data Collection Tools

Data were collected using face-to-face interviews with the Student Individual Information form, Young's Internet Addiction Test-short form (YIAT-SF), Cyberbullying scale (CBS), Cyber Victimization scale (CVS), and Parental Attitudes Scale (PAS).

Student Individual Information Form

This form consists of 28 questions prepared by the researcher to determine the socio-demographic characteristics, computer use areas, and social relationships of the participants.

Young's Internet Addiction Test-Short Form

The scale, developed by Kimberly S. Young, was turned into a short form by Pawlikowski et al. (31). This five-point Likert-type scale (1= Never, 5= Very frequently) consists of 12 items. The internal consistency reliability coefficient of the scale was 0.85. Validity and reliability tests found YIAT-SF to be valid and reliable. The scale did not include any reverse-scored items. A high scale score means a higher degree of internet addiction. YIAT Cronbach's alpha coefficient was found to be 0.86 in the present study. It is a scale that can be applied to adolescents and university students.

Cyberbullying Scale

The four-point (Never, Sometimes, Usually, Always) CBS was developed by Arıcak et al. (27) and consists of 24 items. The lowest scale score was 24 and the highest was 96. A high scale score means a higher level of cyberbullying behavior. It is a scale that can be applied to primary school 4th grade and secondary school 5th, 6th, 7th and 8th grade students (10-14 years old). The Cronbach's alpha coefficient of the scale was 0.95 and test-retest reliability coefficient was 0.70. Based on these values, the scale was reliable (27). The Cronbach's alpha coefficient of the CBS was found to be 0.91 in the present study.

Cyber Victimization Scale

The Cronbach's alpha coefficient was 0.89 and test-retest reliability was 0.75 for this scale, which was developed by Arıcak et al. (32). These values proved the scale to be reliable. The scale consists of 24 items which can be answered "yes" or "no". The lowest scale score is 24 and the highest is 48. It is a scale that can be applied to adolescents [primary, secondary and high school students (between the 5th and 12th grades)]. A high scale point means a higher cyber victimization (32). The Cronbach's alpha coefficient of the scale was found to be 0.90 in the present study.

Parental Attitude Scale

PAS was developed by Lamborn, Maunts, Steinberg and Dornbush (1991). The scale consists of three dimensions: acceptation/attention, control/checking and psychological autonomy. Validity and reliability tests were separately conducted on primary school, high school and university students. The test-retest reliability coefficient and the Cronbach's alpha internal consistency for high school students were respectively: 0.82 and 0.70 for acceptation/attention, 0.88 and 0.69 for control/checking; 0.76 and 0.66 for psychological autonomy (33). The Cronbach's alpha for the PAS sub-scales were: 0.65 for psychological autonomy, 0.71 for acceptance/attention and 0.73 for control/checking.

Ethical Principles

Before data collection, a university Non-Invasive Ethical Committee gave ethical approval (2017.10.05) and official permission (49405861-44.E.2025706). The students and parents were informed about the aim of this study and gave informed consent and written permission.

Procedure

Pre-practice

After the necessary permissions were given, ten students who met the inclusion criteria and were outside of the study were selected for pre-administration in order to determine the clarity of the forms and the time required to complete them.

Practice

The surveys were given to ninth grade students studying at four different high schools. Data were collected using the Student Individual Information Form, YIAT-SF, the CS, the CVS and the PAS through a face-to-face method between the dates of September 2017 and March 2018.

Statistical Analysis

Data were analyzed digitally. Descriptive statistics (number, percentage, mean, and standard deviation), the difference between two means tests parametric (Student's t-test, One-Way ANOVA) and non-parametric (Kruskal-Wallis variance analysis, Mann-Whitney U tests) based on homogeneity tests (Kolmogorov-Smirnov and Shapiro-Wilk) and Bonferroni post-hoc tests were used in the data analysis. Correlation coefficients were used in the comparison of the groups. The Cronbach's alpha coefficients of the scales were calculated. In statistical decisions, $p<0.05$ was accepted as the indicator of a significant difference.

Results

Of the participants, 59.1% were female, 40.9% were male, 90.2% were aged between 13 and 15, 48.9% had three or four siblings, 74.9% had a score of 85 or higher in their primary school diploma grades. Of them, 80.5% had a good family relationship, 68.4% did activities with their families, 69.1% had a hobby and 73.8% had good friendships.

Of the participants' mothers, 60.4% were aged between 36 and 45 years, 36.3% were primary school graduates, 76.9% did not work and 14.2% of those who worked were either civil servants or workers. Of the fathers, 65.4% were aged between 36 and 45 years, 29.1% were high school graduates, 36.4% were either civil servants or workers. Of the families, 77.8% had a nuclear structure, 53.3% had income equal to expenses, and 86.2% had social security.

Of the students, 84.7% had computers or tablets at home, 47.1% had their own personal computer or tablet, 99.3% owned a smartphone. Of them, 57.5% went to sleep between 11:00 p.m. and 12:00 a.m., 44.9% used a computer once a week, 44.9% used computers to watch videos or movies, 57.4% used smartphones to follow social media. Of the students, 25.0% experienced exhaustion and 14.6% headaches after long-term use of technology.

The difference between the students' YIAT-SF mean scores, which was based on the student individual information form, was significant ($p<0.001$). The mean score of those who had good familial relationships was 26.21±9.75 while it was 30.14±10.80 for those with mediocre relationships. No significant difference was found regarding the other characteristics ($p>0.05$) (Table I).

Technology usage characteristics showed that those who had computers or tablets at home and personal computers had higher scale scores than those who did not ($p<0.001$). Those who went to sleep between 01:00 and 02:00 a.m. and who used the internet for more than three hours a day had higher scale scores than those who did not ($p=0.001$).

The CS based on the student individual information form showed no significant difference between the

Table I. Students' mean scores on the Young Internet Addiction Test short-form based on technology use characteristics

Characteristics	n	%	Mean	SD	Test
Home computer/tablet					
Owns	466	**84.7**	27.65	9.94	t=4,009
Does not own	84	15.3	22.94	9.74	**p<0.001**
Personal computer					
Owns	259	47.1	28.49	9.69	t=3,460
Does not own	291	**52.9**	25.55	10.17	**p=0.001**
Bedtime					
20.00-22.00	131	23.8	23.00[a,b,c]	(17.00-30.00)	
23.00-24.00	316	**57.5**	25.00[a,d]	(19.00-33.00)	X^2=31,358
01.00-02.00	88	16.0	30.50[b,d]	(23.00-39.00)	**p<0.001**
03.00 or later	15	2.7	29.00[c]	(25.00-48.00)	
Time spent on computer					
Two or three times a week	152	27.4	27.61[a,e]	9.38	
Once a week	247	**44.9**	23.84[a,b,c,d]	8.92	
Once a day, approximately one hour	61	11.1	28.07[b,f]	10.28	F=18,881
Once a day, approximately three hours	39	7.1	31.18[c]	9.95	**p<0.001**
Once a day, more than three hours	51	9.3	35.25[d,e,f]	10.67	

F: One-Way variance analysis statistics, t: t-test statistics, X^2: Kruskal-Wallis statistics
[a,b,c,d,e,f]According to multiple comparison test (post-hoc: Bonferroni) results, different letters define significant difference between scale scores
SD: Standard deviation

characteristics' scale scores except for gender and family relationships (p>0.05). Females had a lower CS score than that of males (z=-2,313, p=0.021). Those who had good family relationships had higher scale mean scores than those with mediocre relationships. This difference was significant (z=-3,105, p=0.002).

The CS based on the parent individual information form showed no significant difference between the characteristics' scale scores except for the mothers' employment status (p>0.05). Those students who had a working mother had higher scale mean scores than those who did not. This difference was significant (z=-2,662, p=0.008) (Table II).

The students' CS mean scores based on their technology use characteristics illustrated that those who had home computers/tablets or personal computers had higher scale scores than those who did not (respectively: p=0.016, p=0.002). Those who went to sleep between 08:00 and 10:00 p.m. had lower scale scores than those who did not (p<0.001). Those who used the computer each day, for more than three hours had higher scale scores than those who did not (p=0.001).

According to the students' CVS mean scores based on the student individual information form, female students had higher mean scores than male students. This difference was significant (p=0.011). Those with between 85 and 100 primary school diploma grades had lower scale scores than the others (p=0.002). Those who had good family relationships had higher scale mean scores than those with mediocre relationships (p<0.001). According to the parents' CVS mean scores based on the parent individual information form, those students whose fathers were aged between 30 and 35, did not work or were retired and were primary school graduates had higher mean scores than the others (p<0.05). Additionally, those students with less income and more expenses had higher scale mean scores than the others (p<0.05) (Table III).

The students' CVS mean scores based on their technology usage characteristics meant that those who had home computers/tablets or personal computers had lower scale scores than those who did not. This difference was significant (p<0.01). Those who went to sleep between 08:00 and 10:00 p.m. and used the computer once a week had higher scale scores than those who did not (p=0.001) (Table IV).

The Parental Attitude sub-scale mean scores of the students based on their technology usage characteristics illustrated that those who spent time on a computer two or three times a week had a higher psychological autonomy sub-scale scores than the others. This difference was significant (p=0.030). Those who did not have personal computers had higher acceptation/attention sub-scale scores than those who did. This difference was significant (p=0.003). Those who used the computer once a day and for more than three hours had lower control/checking sub-

Table II. Students' mean scores on the cyberbullying scale based on technology use characteristics

Characteristics	n	%	Median	25th-75th percentile	Test
Home computer/tablet					
Owns	466	84.7	24.00	(24.00-27.00)	z=-2,401
Does not own	84	15.3	24.00	(24.00-25.75)	**p=0.016**
Personal computer					
Owns	259	47.1	25.00	(24.00-27.00)	z=-3,076
Does not own	291	52.9	24.00	(24.00-26.00)	**p=0.002**
Bedtime					
20.00-22.00	131	23.8	24.00[a,b,c]	(24.00-25.00)	
23.00-24.00	316	57.7	24.50[a]	(24.00-27.00)	X^2=19,859
01.00-02.00	88	16.0	25.00[b]	(24.00-27.75)	**p<0.001**
03.00 or later	15	2.7	26.00[c]	(24.00-37.00)	
Time spent on computer					
Two or three times a week	152	27.6	25.00[a]	(24.00-27.00)	
Once a week	247	44.9	24.00[a,b]	(24.00-26.00)	
Once a day, approximately one hour	61	11.1	24.00	(24.00-27.00)	X^2=17,612
Once a day, approximately three hours	39	7.1	25.00	(24.00-28.00)	**p<0.001**
Once a day, more than three hours	51	9.3	26.00[b]	(24.00-30.00)	

X^2: Kruskal-Wallis statistics, z: Mann-Whitney U test z statistics
[a,b,c]According to multiple comparison test (post-hoc: Bonferroni) results, different letters define significant difference between scale scores

scale scores than the others. This difference was significant (p<0.001).

The students' PAS mean scores meant that the female students with a hobby, primary school diploma grades between 85 and 100 and who spent time on a computer two or three times a week had significantly higher psychological autonomy sub-scale scores than the others (Table V).

The correlation between YIAT-SF and CBS (r=0.335) was a positive weak relationship; and a negative weak relationship (r=-0.345) between CVS. The correlation between the sub-scales' psychological autonomy and control/checking (r=-0.193; r=-0.158) were negative very weak relationships and there was a positive very weak relationship between the acceptation/attention (r=0.231) sub-scale. There was a negative moderate relationship between the CBS and CVS (r=-0.436); a negative very weak relationship between the psychological autonomy and control/checking sub-scales (r=-0.112; r=-0.182); and a positive very weak relationship between the acceptation/attention sub-scale (r=0.159). There was a positive very weak correlation between the CVS and the psychological autonomy and control/checking sub-scales (r=0.148; r=0.157) and a negative very weak linear relationship with the acceptation/attention sub-scale (r=-0.200). There was a positive very weak relationship between the psychological autonomy and the acceptation/attention sub-scales (r=0.153); and a negative weak relationship between the acceptation/attention and the control/checking sub-scales (r=-0.280).

Discussion

Parental attitudes were observed to affect adolescents' virtual behaviors such as being exposed to cyberbullying and thus, cyber victimization. According to the Global Digital Analysis report (2019) (34), there were 4.39 billion internet users in the world. Of them, 59.36 million were located in Turkey. The internet use frequency in Turkey in the 16-74 age group was 48.9% in 2013, 61.2% in 2016 and 72.9% in 2018. Of the 2018 internet users, 80.4% were male and 65.55% were female (35). Almost all students included in this study used the internet (99.5%). Of these students, 84.7% had computers or tablets at home, 47.1% had a personal computer or tablet, 99.3% owned a smartphone and 44.9% used the computer once a week. Parents also provided their children with the opportunity to use smart phones with internet access, which they bought with the intention of being able to reach their children at any time during the day and to ensure their safety, anywhere, and at any time of the day (36). Children experience negative experiences such as cyberbullying and cyber victimization as well as positive achievements such as learning new things, accessing information by using smart phones with internet access (37). Of them, 25% experienced exhaustion and 14.6% experienced headaches after long-term use of technology. Another study found a parallel increase

Table III. Students' mean scores on the cyber victimization based on technology use characteristics

Characteristics	n	%	Median	25th-75th percentile	Test
Home computer/tablet					
Owns Does not own	466 84	84.7 15.3	47.00 48.00	(44.00-48.00) (47.00-48.00)	z=-3,173 **p=0.002**
Personal computer					
Owns Does not own	259 291	47.1 52.9	47.00 48.00	(44.00-48.00) (46.00-48.00)	z=-3,826 **p=0.001**
Bedtime					
20.00-22.00 23.00-24.00 01.00-02.00 03.00 or later	131 316 88 15	23.8 57.5 16.0 2.7	48.00[a] 47.00 46.00[a] 47.00	(46.00-48.00) (44.25-48.00) (43.00-48.00) (42.00-48.00)	X^2=15,787 **p<0.001**
Time spent on computer					
Two or three times a week Once a week Once a day, approximately one hour Once a day, approximately three hours Once a day, more than three hours	152 247 61 39 51	27.6 44.9 11.1 7.1 9.3	47.00 48.00[a] 47.00 46.00 47.00[a]	(44.00-48.00) (46.00-48.00) (45.00-48.00) (42.00-48.00) (43.00-48.00)	X^2=19,428 **p<0.001**

X^2: Kruskal-Wallis statistics, z: Mann-Whitney U test z statistics
[a]According to multiple comparison test (post-hoc: Bonferroni) results, different letters define significant difference between scale scores

Table IV. Students' sub-scale mean scores of the parental attitudes scale based on socio-demographic characteristics

Variables	n	%	Psychological autonomy	Acceptation/Attention	Control/Supervision
			Mean±SD	Median 25th-75th percentile	Median 25th-75th percentile
Sex					
Female Male	325 225	**59.1** 40.9	21.18±4.54 20.27±5.20	16.00 (13.00-18.00) 16.00 (13.00-18.00)	23.00 (21.00-25.00) 21.00 (19.00-23.00)
			t=2,113 **p=0.035**	z=0.287 **p=0.774**	z=-6,338 **p<0.001**
Age					
13-15 16-17	496 54	**90.2** 9.8	20.86±4.84 20.33±4.779	15.00 (13.00-18.00) 17.00 (14.00-19.25)	23.00 (21.00-25.00) 21.50 (18.75-24.00)
			t=0.760 p=0.448	z=-2,138 **p=0.033**	z=-2,204 **p=0.027**
Number of siblings					
1-2 3-4 5 or more	240 269 41	43.6 **48.9** 7.5	20.81±5.01 20.85±4.59 20.56±5.48	15.00 (13.00-18.00) 16.00 (13.00-19.00) 15.00 (13.00-18.00)	23.00 (20.00-24.00) 23.00 (21.00-25.00) 23.00 (20.50-25.00)
			F=0.062 p=0.940	X^2=5,207 p=0.074	X^2=0.864 p=0.649
Primary school diploma grade					
45-69 70-84 85-100	35 103 412	6.4 18.7 **74.9**	18.06a±6.30 20.04±4.38 21.24a±4.71	17.00 (13.00-21.00) 17.00a (14.00-21.00) 15.00a (13.00-18.00)	23.00 (19.00-25.00) 23.00 (21.00-25.00) 23.00 (20.00-24.00)
			F=8.827 **p<0.001**	X^2=15,502 **p=0.002**	X^2=0.612 p=0.736
Relationship with the family					
Good Moderate	443 100	**80.5** 18.2	20.96±4.90 20.09±4.61	15.00 (12.00-17.00) 19.00 (16.00-22.00)	23.00 (21.00-25.00) 21.00 (19.00-23.00)
			t=1.616 p=0.107	z=-7,775 **p<0.001**	z=-4,333 **p<0.001**
Activities with family					
Yes No	376 174	**68.4** 31.6	20.80±5.00 20.83±4.47	14.00 (12.00-17.00) 18.00 (15.00-21.00)	23.00 (21.00-25.00) 22.00 (20.00-25.00)
			t=0.061 p=0.951	z=-8,740 **p<0.001**	z=-1.503 p=0.133
Hobby					
Yes No	380 170	**69.1** 30.9	21.14±4.72 20.08±5.01	15.00 (13.00-18.00) 16.00 (13.00-20.00)	23.00 (21.00-25.00) 23.00 (20.00-25.00)
			t=2,367 **p=0.018**	z=-2,188 **p=0.029**	z=-0.723 p=0.470
Relationship with friends					
Good Moderate Poor	406 133 11	**73.8** 24.2 2.0	21.00(18.00-24.00) 21.00(18.00-24.00) 23.00(19.00-24.00)	15.00[a] (12.75-18.00) 17.00[a] (13.00-20.00) 16.00 (13.00-21.00)	23.00[a] (21.00-25.00) 22.00[a] (20.00-23.00) 21.00 (15.00-23.00)
			X^2=1.158 p=0.560	X^2=10,884 **p=0.004**	X^2=12,054 **p=0.002**

F: One-Way variance analysis, t: Kruskal-Wallis, z: Mann-Whitney U
[a]According to multiple comparison test (post-hoc: Bonferroni) results, different letters define significant difference between scale scores

between physical problems and time and frequency of internet use. Some of the most common problems were fatigue and redness of the eyes, head, neck, back, joint and muscle pains; insomnia and exhaustion (38-40). The present study found a significant relationship between the students' family relationships and internet addiction scores (p<0.001). Those with good family relationships had a lower scale score than those who had mediocre family relationships. One study found that students who did not have a positive or desirable relationship with their family had higher levels of internet addiction (41). Those students whose mothers were housewives had lower levels of internet addiction than those with mothers who were either state employees or workers (p<0.05). It is thought that since the mother is always at home as a housewife, she can control the time and frequency of her child's computer use, thus preventing internet addiction. It has been reported that parental behavioral control, parental psychological control, and parent-child relational qualities are effective in reducing adolescent internet addiction (42,43). The students' YIAT-SF mean scores based on their technology use showed that those who had home computers or tablets (p<0.001), personal computers, who went to sleep late (01:00 to 02:00 a.m.) and who used the computer once a day for more than three hours (p<0.05); had higher mean scores. The study by Yang and Tung (44) found internet addiction to be higher in those who spent longer times on the internet. These findings are parallel to this study's findings. Students who have their own computers and tablets can access the internet more easily whenever they want. This situation allows students who sleep late at night to spend more time on the internet. These are the primary reasons why internet addiction is higher among these students.

No significant difference was found between the students in terms of internet addiction based on their purpose of using a computer or smartphone (p>0.05). However, 44.9% of the students used computers to watch videos or movies and 57.4% used smartphones to follow social media. The most common reason for internet use was found to be social media (9,10,45).

Cyberbullying was more common among male students (p<0.05). In line with the present study, many studies found cyberbullying rates to be higher in male students than females (20,46). This result can be attributed to the fact that men use more technological tools and have less control systems due to their gender perspective. The cyberbullying rates of those with good family relationships were higher than those with mediocre family relationships (p<0.05). This interesting result can be interpreted as some students who have good relations with their parents tend to cyberbully because of the encouragement they get from parental support. Some literature shows the opposite to the results of this study. According to studies by Gómez-Ortiz et al. (47), the rates of cyberbullying in students with good family relationships decreased and Ybarra et al. (48) found the students with weak family relationships had higher cyberbullying rates.

The present study found that those students who had home computers or tablets or personal computers went to sleep at 03:00 a.m. or later, and who used the internet for more than three hours each day had higher cyberbullying rates than others (p<0.05). This study's findings are in line with the literature. The higher the internet usage time is, the higher the cyberbullying rate (49). Those students with home computers or tablets or personal computers were able to commit more cyberbullying than others due to easier access to the internet. The more time which is spent on the internet means higher cyber victimization (36). CVS scores of the female students were higher than those of males (p<0.05). Contrary to this result, another study found

Table V. Correlation between scale mean scores

	Young's Internet Addiction Test-short form	**Cyberbullying scale**	**Cyber Victimization scale**	**Psychological Autonomy Sub-scale**	**Acceptation/ Attention Sub-scale**	**Control/ Checking Sub-scale**
Young's Internet Addiction Test-short form	1.000					
Cyberbullying scale	**0.335***	1.000				
Cyber Victimization scale	**-0.345***	**-0.436***	1.000			
Psychological Autonomy Sub-scale	**-0.193***	**-0.112***	**0.148***	1.000		
Acceptation/Attention Sub-scale	**0.231***	**0.159***	**-0.200***	**0.153***	1.000	
Control/Checking sub-scale	**-0.158***	**-0.182***	**0.157***	-0.069	**-0.280***	1.000

*p<0,05

male students to be exposed to more cyber victimization as they spend more time on the internet (9). There is one study that found that male students experience more cyber victimization than females (46). According to the present study results, those with a primary diploma grade between 85 and 100 experienced cyber victimization on a lower level than others ($p<0.05$). Those students whose diploma grades were lower due to more time spent on the internet experience more cyberbullying. Those students with good family relationships had higher cyber victimization rates ($p<0.001$). In another study, the cyber victimization rates of students with weak family relationships was found to be higher (48). It has been stated that students whose general family functions are increased will reduce their cyberbullying and cyber victimization experiences due to their internet addiction (37,49).

The Parental Attitude sub-scale mean scores of the students based on their technology usage characteristics show that female students with a hobby and a primary diploma grade between 85 and 100 had higher psychological autonomy sub-scale scores than the others. This difference was significant ($p=0.001$). Female students and those with high diploma grades perceived their parents' attitude as democratic and positive, which resulted in them being psychologically more autonomous and successful. Having a hobby leads children to be busy with something they love doing and form their own personal space, making them feel psychologically more autonomous.

Students who had no hobbies and mediocre friendships had higher family acceptation/attention mean scores than others and this difference was significant ($p<0.05$). Families might have improved their acceptation/attention attitudes to prevent their children from feeling socially incompetent.

Of the female students, those aged between 13 and 15 and having good family relationships had higher control/checking sub-scale mean scores than the others. This difference was significant ($p<0.05$). An increase in the parents' control over the younger age groups and females might be due to the parents' controlling tendencies. Of the students, those who had good friendships were controlled/checked more by their parents ($p<0.05$). Parents might have increased their controlling/checking attitudes so as to prevent children from risky situations with friendships. In conclusion, it was revealed that family control and warmth in male students' families were low and as the grade increased, family control and warmth decreased.

The Parental Attitudes sub-scale mean scores of the students based on their technology usage characteristics meant that those who spent time on a computer two or three times a week had higher psychological autonomy sub-scale scores than the others, and those who used the computer more than three hours each day had lower control/checking mean scores. This difference was significant ($p<0.05$). The more frequently a child uses a computer and the internet, the greater the parents' control over the child. On the other hand, as the child uses the computer less frequently, their parents' control over the child decreases, which in turn increases the child's psychological autonomy.

The relationship between the YIAT-SF, CBS, CVS and PAS indicated that cyberbullying scores increased in line with internet addiction scores ($p<0.05$). A high internet addiction score meant a lower cyber victimization score. A high YIAT meant a low psychological autonomy and control/checking score. A high internet addiction score meant a high acceptation/attention score. In one study, it was determined that as the democratic parental attitudes of the students increased, the tendency to violence decreased, and as the protective and authoritarian attitudes increased, the tendency to violence increased (50). In the study by Altıntaş ve Öztabak (51), problematic internet usage levels were lower in those whose parents had democratic parental attitudes.

The higher the cyberbullying score, the lower the cyber victimization score, although one study suggested a significant and positive relationship between cyberbullying and cyber victimization (25). Perceived social support from the family and parental supervision of internet use decreases cyberbullying rates (52,53). In a meta-analysis study, a significant correlation was found between parental monitoring and cyberbullying (29). The present study found that high cyberbullying scores indicated high acceptation/attention scores and low psychological autonomy and control/checking scores. Those students who have less controlling and more accepting parents may tend more towards cyberbullying due to low parental supervision. High cyber victimization scores indicated high psychological autonomy and control/checking scores and low acceptation/attention scores. In one study, there was found to be a relationship between the parents' attitudes and the adolescents' cyberbullying levels (14). Parental control includes family guidance, stopping certain internet-related behaviors and establishing rules for internet use (54). Those students with more controlling parents had less tendencies towards cyberbullying and were less exposed to cyber victimization (53). In another study, it was found that adolescents who had parents with democratic attitudes

experienced less cyberbullying and victimization than those with negligent and or authoritative attitudes (55). Altıntaş and Öztabak (51) found a positive relationship between overuse and problematic internet use of individuals with protective, demanding and authoritarian style families and found a low negative relationship with democratic style families. One study found that controlling parents and inconsistent internet mediation styles were associated with a higher prevalence of cyberbullying (56). High acceptation/attention sub-scale scores meant high psychological autonomy and low control/checking sub-scale scores. Poor parental attitudes led to cyber harm and those parents with suppressive and authoritative attitudes played a role in cyberbullying (47). Adolescents who do not have a healthy and warm relationship with their parents try to compensate for the lack of communication that is present in the family through virtual relationships (52).

These types of virtual relationships cause a greater risk of exposure to cyber victimization. Adolescents try to obtain the attention that is missing in their daily lives through bullying (14). Yiğit et al. (49) found that students with high social support levels did not commit cyberbullying and had lower levels of exposure to such behaviors. Positive emotional support from the family, defined as trust, communication, secure attachment, and a lack of alienation between the parents and their children, has been shown to be a protective factor that lowers the likelihood that an individual will perpetrate cyberbullying (13).

Parental attitude plays a significant role in forming and developing a child's personality. The interaction within the family plays a significant role in the child's personality and emotional development (57). The interaction between the parents and their children allows for the safe and efficient use of the internet and reduces negative risks (58). Parents must provide the emotional warmth that can support an adolescent's disclosure of online activity (13). Parenting roles and guidance are important in controlling a child's internet usage, and this can be supported by internet literacy education at home and at school (59).

As adolescents' habits such as internet addiction, cyberbullying and victimization might continue and affect their lives in the future, (9,24) families should seek professional help on this subject. The public health prevention model provides a framework to organize school nurses' interventions in order to prevent, reduce, and manage incidents of cyberbullying perpetrated via social media. This framework consists of three levels (primary, secondary, and tertiary) but best practice states that interventions on the primary and secondary levels are the most effective in reducing rates of cyberbullying (60). School nurses have the opportunity to help address this problem. To do so, school nurses need to be well versed in recognizing social media, understanding the terminology, and using common social media apps (61).

Study Limitations

The limitations of the present study should be taken into consideration in the interpretation and generalization of the findings obtained within the content of this study. It is limited to the information obtained from the sample group and the data collection tools used.

Conclusion

Consequently, risky internet usage and internet addiction are high among students. Adolescents' internet usage and increases in their internet addiction levels, their experiences of cyberbullying and victimization and parental attitudes regarding these behaviors are presented through the findings of this study.

School health nurses should determine high-risk groups for internet addiction, cyberbullying and cyber victimization and develop intervention programs for those students who are at high risk, for their families and for their teachers. Training which emphasizes parental roles should be developed regarding the issues of cyberbullying and cyber victimization. Teachers and administrators should be informed about the importance of students' friendships, socio-cultural activities and hobbies in preventing problems such as internet addiction and cyberbullying; and they should work cooperatively to encourage students to socialize more. Studies should be carried out in schools encouraging school administration, teachers, counselors, psychologists, doctors and nurses to take a more active role in decreasing rates of internet addiction and cyberbullying.

Ethics

Ethics Committee Approval: Ethics committee approval was received for this study from the Nevşehir Hacı Bektaş Veli University (date: 27.10.2017, approval no: 2017.10.05).

Informed Consent: Informed written consent was obtained from the mothers participating in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: D.E., Design: D.E., Supervision: D.E., N.G.B., Resources: K.A.N., Materials: K.A.N., Data Collection and/or

Processing: K.A.N., Analysis and/or Interpretation: K.A.N., D.E., Literature Search: K.A.N., D.E., Writing: D.E., Critical Review: D.E., N.G.B.

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Original Article

Monitoring the Quality of Life in Dyspeptic Children with KINDL Scale

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ABSTRACT

Aim: We aimed to evaluate quality of life in functional and organic dyspepsia and its change during follow-up.

Materials and Methods: Children between 4-17 years of age with dyspeptic complaints were enrolled into this study. Organic and functional dyspepsia were differentiated based on clinical findings and the findings of upper gastrointestinal endoscopy, if performed. The Kinder Lebensqualität Fragebogen (KINDL) questionnaire was conducted when the patients were referred to hospital and at their 1st and 3rd month visits, prospectively. Both groups were compared with regard to their demographic data, symptoms and quality of life scores. Factors which affected the KINDL results and any changes in the KINDL scores during follow-up were evaluated.

Results: The study group consisted of 71 functional dyspepsia and 65 organic dyspepsia patients. The mean quality of life scores in the physical wellness and school subscales were higher among the functional dyspepsia patients. The total score of the functional dyspepsia group was higher. There was no relation between the individual's gender, their number of symptoms and their KINDL scores. At the first month visit, the total scores and mean scores of the self-esteem, family, school and friends subscales were higher in the functional dyspepsia group. At the third month visit, the mean self-esteem score was higher in the functional dyspepsia group. Total scores increased significantly during follow-up in both the organic dyspepsia and functional dyspepsia groups. This increase was higher in the organic dyspepsia group.

Conclusion: Quality of life in both functional dyspepsia and organic dyspepsia patients is affected; applying recommendations and treatment increased the quality of life of both groups. A quality of life scale can be used to monitor response to treatment.

Keywords: Children, follow-up, functional dyspepsia, quality of life, organic dyspepsia

Introduction

Dyspepsia is a common upper gastrointestinal clinical symptom group resulting from various causes with a wide range of symptoms and signs. Symptoms such as abdominal discomfort, epigastric pain or burning, postprandial fullness, or early satiety are defined as dyspepsia (1-3). Sometimes bloating, heartburn, or nausea may also be present (4). Dyspepsia may be due to various reasons such as peptic ulcer disease, gastrointestinal lesions due to non-steroid anti-inflammatory drugs, or non-organic non-ulcer functional reasons (1-3).

Quality of life (QoL) is defined as the individual daily life responses to any physical, mental and social impacts of a disease which affect individual satisfaction in certain life conditions. QoL scales are used to identify in which dimensions children with various chronic complaints and

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developmental problems are affected by their disease or any therapeutic interventions regarding their condition (5). Dyspepsia is one of these conditions which has a negative impact on QoL. Studies have shown that children with functional dyspepsia (FD) have a lower QoL in comparison to healthy children. However, there is little data regarding their QoL after treatment (6).

In this study, we aimed to monitor the QoL of patients with functional and organic dyspepsia (OD) by means of an age appropriate Kinder Lebensqualität Fragebogen (KINDL) scale during their follow-up and also to evaluate whether there are any differences between these two groups in terms of their QoL.

Materials and Methods

In this study, the QoL of children with organic and functional dyspepsia was evaluated via the KINDL scale before and after treatment. Patients between 4 and 17 years of age with dyspepsia who were admitted into the pediatric gastroenterology outpatient clinic of Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital between April 2015 and October 2015 and who agreed to participate were enrolled into this study. Pain or burning in the epigastrium, postprandial fullness or early satiety were accepted as dyspeptic complaints (1,2). Those patients with chronic diseases other than dyspepsia were excluded as these complaints might also affect their QoL. A minimum of 64 patients were planned to be included into both the organic and functional dyspepsia groups considering a power size of 80% and an effect size of 50%. A thorough history and physical examination was performed. After clinical evaluation, patients were accepted as having functional dyspepsia if there was no evidence of an organic disease. The diagnosis of FD was made based on a thorough history, examination and by clinical judgment, the presence of alarm signs, and a selection of the appropriate tests based on response to treatment. Upper gastrointestinal system endoscopy was performed if the complaints persisted or relapsed after appropriate treatment, or if there were any alarm symptoms. Unfortunately, consent for endoscopy could not be obtained from all families. If there was gastritis, ulcer or *Helicobacter pylori* infection, the patient was accepted as having OD. The presence and duration of dyspeptic symptoms, other accompanying symptoms, and constipation were investigated. Appropriate management was arranged by a gastroenterologist. Patients were followed up for three months. The functional and organic dyspepsia groups were compared with regard to their demographic data, symptoms and QoL scores. Factors which affected the KINDL results and any change in the KINDL scores during follow-up were evaluated.

Disease appropriate treatment was given to each patient. If the patient was accepted as having FD, proton-pump inhibitors were prescribed to those patients with epigastric pain or burning predominantly. Prokinetic agents were given if there was early satiety or postprandial fullness. More frequent and smaller meals, and the avoidance of caffeine, fatty foods and spicy foods were recommended.

KINDL is a QoL scale used widely in children. It may show both the dimensions which are affected by the disease and the disease effect before and after treatment (7-9). It has different versions for 4-7 years, 8-12 years and 13-16 years of age. It contains six subscales and a total of 24 Likert-scaled items. These are physical well-being, emotional well-being, self-esteem, family, friends and school. Scores, which can vary between 0-100, are calculated for each subscale and for the total (10). Higher scores indicate a better QoL. The Turkish validated version of this scale was used in our study (11). The KINDL questionnaire was applied at their first referral and at the first-month and third-month visits.

Written informed consent was signed by the parents or caregivers who were the legal guardians of each participant.

Statistical Analysis

SPSS (Statistical Package for Social Sciences) 22.0 for Windows program was used for statistical analysis. Significance was accepted as $p<0.05$. The mean, standard deviation and percentage distribution data were used for descriptive data and KINDL scores. The chi-squared test was applied for comparison of alarm symptom distribution and school absenteeism. Independent-samples t-test was used to compare the total KINDL scores and the factors affecting the KINDL scores. Analysis of variance was used for repeated measures in the comparison of the total scores during the follow-up of each group. Ethical approval was obtained from Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital Ethics Committee on April 9th, 2015 (no: 2015-7229).

Results

During the study period, 214 patients with dyspepsia were admitted into the gastroenterology outpatient clinic. The study group consisted of 136 patients who were eligible and agreed to participate in this study. Of these, 71 were assigned to the FD group and 65 to the OD group. All of the participants completed the study. There were 97 girls

(71.3%) and 39 boys (28.7%). The mean age of the patients in the study was 12.7±3.3 years. The mean age of the OD group was higher (13.8±2.6 years vs. 11.5±3.6 years, p<0.01). There was no gender difference between the two groups (p>0.05). Table I shows symptom distribution and mean duration of complaints in the OD and FD groups. The mean duration of symptoms was similar in both groups (p>0.05). Symptom rates were not different between the OD and FD groups (p>0.05). School absenteeism was also similar (52.3% vs. 49.3%, p>0.05).

Upper gastrointestinal endoscopy (UGE) was performed in 38 (27.9%) patients in the OD group. Of these, 14 patients had severe gastritis according to macroscopic and microscopic findings. One patient also had esophagitis.

The mean scores of the physical well-being and school dimensions were higher in the FD group than that of the OD group (p<0.05). There were no differences between the two groups in the friends, emotional well-being, self-esteem and family dimensions (p>0.05). The mean total score was higher in the FD group in comparison to the OD group (63.9±14.0 vs. 58.7±12.1, p<0.05) (Table II).

Table I. Duration of symptoms in the organic and functional dyspepsia groups

Symptoms (n)	Symptom duration (month) (mean±SD)	p-value
Abdominal pain Functional dyspepsia (71) Organic dyspepsia (65)	 12.1±9.9 14.8±13.9	0.183
Nausea Functional dyspepsia (48) Organic dyspepsia (42)	 11.5±9.4 12.3±12.1	0.723
Bloating Functional dyspepsia (40) Organic dyspepsia (36)	 11.6±8.8 10.7±11.5	0.695
Flatulence Functional dyspepsia (39) Organic dyspepsia (29)	 10.4±9.2 13.4±13.2	0.283
Vomitting Functional dyspepsia (25) Organic dyspepsia (23)	 10.1±10.6 8.3±8.8	0.511
Heartburn Functional dyspepsia (36) Organic dyspepsia (37)	 12.5±10.0 11.3±11.0	0.628
Constipation Functional dyspepsia (7) Organic diyspepsia (3)	 10.1±3.2 16.0±7.0	0.092
Stress Functional dyspepsia (40) Organic dyspepsia (38)	 9.8±5.6 9.4±5.7	0.753
Regurgitation Functional dyspepsia (30) Organic dyspepsia (30)	 12.8±9.2 11.6±8.7	0.625

SD: Standard deviation

A negative correlation was observed between the initial KINDL total score and age in both the OD and FD groups (p<0.05). There was no significant relation between gender and the number of symptoms with respect to the KINDL scores (p>0.05).

The mean scores of the self-esteem, family, school, and friends subscales and the mean total score were higher in the FD group compared to the OD group at the first month visit (p<0.05). There was no difference between the groups in terms of physical well-being (p>0.05) (Table II).

The mean score of self-esteem was higher in the FD group (p<0.05). However, there was no difference between the two groups in terms of the physical well-being, emotional well-being, friends, family and school dimensions at the third month visit (p>0.05, Table II).

During the follow-up, the total QoL scores gradually increased in both groups (Figure 1). There was no difference between the groups in terms of the mean third month total scores (p>0.05). The first and last KINDL scores were significantly different in both groups (p<0.01). However, a higher increase was observed in the OD group compared to the FD group.

Dyspepsia improved in 88 (64.7%) patients while complaints continued in the rest. The KINDL scores in the physical well-being (21.3±3.1 vs. 18.4±2.0) and friends (17.6±2.5 vs. 15.8±1.7) dimensions were higher in those patients whose complaints still persisted during the final visit (p=0.010 and p=0.015, respectively). The final school dimension (19.1±2.1 vs. 18.7±2.8) and the total KINDL scores (11.4±1.2 vs. 10.7±1.5) were higher in those patients whose dyspepsia was resolved (p=0.004 and p=0.001, respectively).

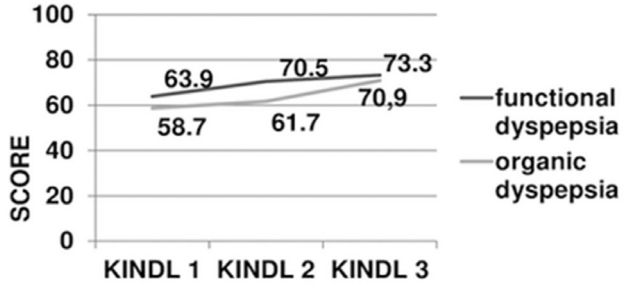

Figure 1. The KINDL total scores in organic and functional dyspepsia groups during follow-up

Discussion

Functional and organic gastrointestinal diseases have a negative impact on QoL. This effect may be more prominent in functional diseases (12,13). However, little is known about QoL after treatment.

Dyspepsia includes symptoms such as early satiety, abdominal pain, epigastric discomfort and postprandial fullness (1,2). Only one third of dyspeptic patients have an underlying organic disorder. This group is classified as OD (1). The rest of the patients have FD. Abdominal pain related functional gastrointestinal disorders are mostly seen in females (14,15). In OD, there is no difference between genders (16,17). Girls constituted the majority of both groups in our study. The mean age of the patients in this study was similar to ages reported in other studies (18,19).

The cause of dyspepsia did not have an impact on the duration or frequency of the dyspeptic complaints. There was no difference between the two groups in terms of dyspeptic symptom rates either. Therefore, we suggest that although there are no organic reasons, complaints in FD might be more frequent and longer lasting, which will affect the QoL.

Gastrointestinal complaints affect children's lives in many different ways. School absenteeism is one of them. School absenteeism is more common in both organic and functional gastrointestinal diseases compared to healthy children. However, in functional and organic gastrointestinal diseases, school absenteeism has been reported at similar rates (20). We also did not note any difference between OD and FD in terms of school absenteeism.

Studies have shown that QoL is affected more in functional gastrointestinal diseases than in organic gastrointestinal diseases (6,12,13,20). In our study, QoL scores were low in both the OD and FD groups. This effect was more prominent in dyspepsia with organic causes. The difference was particularly evident in the physical well-being and school dimensions. We suppose that the complaints of the OD patients may be more severe in our population.

A negative correlation was observed between the initial KINDL total score and age in both groups. It is assumed that as patients grow older, complaints are better perceived and the questions are answered more precisely.

The KINDL scores at the first month visit show that the OD group was still affected more. This effect was present in all dimensions except for the physical well-being dimension. Patients responded similarly after one month of treatment. Except for the physical well-being dimension, as it is a

Table II. KINDL scores at referral, first and third month visits

	Referral		**First month visit**		**Third month visit**	
	Mean±SD	**p-value**	**Mean±SD**	**p-value**	**Mean±SD**	**p-value**
Physical well-being Functional dyspepsia Organic dyspepsia	50.0±25.4 39.9±17.3	**0.008**	60.8±24.3 53.8±19.8	0.066	70.0±23.1 74.3±15.5	0.204
Emotional well-being Functional dyspepsia Organic dyspepsia	67.8±18.3 64.1±20.3	0.272	73.5±18.8 66.8±20.6	0.050	77.2±17.4 79.7±15.5	0.377
Self-esteem Functional dyspepsia Organic dyspepsia	59.4±23.0 52.3±25.5	0.090	66.1±22.7 54.2±22.5	**0.003**	70.2±20.2 59.3±18.9	**0.001**
Family Functional dyspepsia Organic dyspepsia	77.6±22.0 73.6±20.9	0.281	81.3±18.5 74.0±17.7	**0.020**	80.0±17.1 79.2±16.2	0.062
Friends Functional dyspepsia Organic dyspepsia	71.0±21.7 72.0±17.4	0.753	78.8±16.3 67.2±18.4	**<0.001**	80.0±17.1 76.3±16.3	0.203
School Functional dyspepsia Organic dyspepsia	56.8±23.0 48.6±21.7	**0.045**	60.9±22.4 52.5±18.5	**0.025**	56.4±21.6 53.9±16.8	0.467
Total score Functional dyspepsia Organic dyspepsia	63.9±14.0 58.7±12.1	**0.022**	70.5±14.8 61.7±12.8	**<0.001**	73.3±12.6 70.9±10.3	0.215

KINDL: The Kinder Lebensqualität Fragebogen, SD: Standard deviation

more objective finding, we observed improvements in the other dimensions over time. In another study in which the Pediatric Quality of Life scale was used, it was seen that physical health, social functions and school functions were lower in those patients with functional gastrointestinal diseases in comparison to those patients with organic diseases (12). This difference may be due to the different scales used and the social characteristics of the patients in that study. At the third month visit, the difference in the QoL total scores between the functional and organic dyspepsia groups had disappeared. The difference in the subgroup of self-esteem might have been influenced by the current mood of the patients.

A continuous increase was observed in the QoL scores in the OD and FD groups during follow-up. There are many studies about the effects of functional and organic gastrointestinal diseases on QoL. However, there is only one study about the effects during follow-up. That study revealed improvements in the QoL scores of patients with FD in the initial, first and third month visits after treatment (20). Similar increases in the QoL scores were observed in our study. While a gradual increase and significant improvement was observed in the FD group at each follow-up visit, the OD group presented a more distinct improvement after the first month. The improvements in the QoL scores in the follow-up visits indicate that the recommendations and treatment given had successful outcomes.

Improvement in the physical well-being and friends dimensions were significant even in those patients whose complaints persisted. This may indicate that even when there is no complete improvement in complaints, the quality of life may improve due to the proper recommendations. Improvements in complaints led a better QoL in the school dimension. When the total scores were analyzed, QoL improved after treatment in line with recovery as expected.

Study Limitations

This study has some limitations. Firstly, UGE was not performed on all patients, therefore, we might have missed an organic pathology. However, it is an invasive procedure and it is not mandatory in the diagnosis of functional diseases. UGE was recommended in the presence of dysphagia, persistent symptoms or recurrent symptoms after the cessation of drugs (2). We performed UGE in all cases with these recommended indications. The second limitation regards the treatment of FD. There is no one and only proven therapy for functional gastrointestinal diseases. Avoidance of some medications and foods, antisecretory agents and prokinetics may be given according to clinical symptoms (2,21). Tricyclic antidepressants may be recommended in anxious children (3). We treated these patients according to their predominant symptoms and the recommendations in the literature.

Conclusion

Our study showed that the QoL of patients with both functional and organic dyspepsia was positively affected. Therefore, we suggest that appropriate recommendations and treatments should be provided as these may increase QoL. We observed favorable results when OD patients were treated according to their underlying disease. Treatment is important in both disease groups and QoL scales can be used during follow-up to monitor treatment response.

Ethics

Ethics Committee Approval: Ethical approval was obtained from Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital Ethics Committee on April 9th, 2015 (no: 2015-7229).

Informed Consent: Written informed consent was signed by the parents or caregivers who were the legal guardians of each participant.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: E.K.T., O.T., İ.G., Design: E.K.T., O.T., İ.G., Data Collection and/or Processing: E.K.T., O.T., İ.G., Analysis and/or Interpretation: İ.G., E.E., Literature Search: E.E., O.T., Writing: E.K.T., Ö.B.S., O.T., İ.G., E.E.

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

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Original Article

The Effects of Face Mask Usage on Ocular Structures in Children During the COVID-19 Pandemic

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ABSTRACT

Aim: To determine the effects of face mask usage on ocular structures in children during the coronavirus disease-2019 (COVID-19) pandemic.

Materials and Methods: Forty-two children's ocular data from the pandemic period were compared with the same children's ocular data from the pre-pandemic period.

Results: Their mean age was 14.6±2.1 (9-18) years initially. The tear film break-up time values of the children with a mask in the pandemic period were significantly shorter than those of the children without a mask in the pre-pandemic period (9.35±1.40 vs. 12.10±1.05 seconds, p=0.033). There was no staining in any case in the pre-pandemic period, while minimal punctate epithelial corneal staining pattern was determined in 4 (9.5%) children in the pandemic period. The Schirmer test 1 value detected in the pandemic period was similar to the value detected in the pre-pandemic period (11.14±2.07 vs. 12.03±1.01 mm, p=0.127). Additionally, there were no significant changes in visual acuities, central corneal thicknesses, anterior chamber depths, lens thicknesses, and axial lengths between the pre-pandemic and pandemic periods (p>0.05).

Conclusion: To the best of our knowledge, this is the first study to date to evaluate the effects of face mask usage on ocular structures in just children. The use of face masks may cause increased tear evaporation and dry eye in pediatric cases. Educating children about the correct use of face masks can be important. Thus, possible ocular surface changes which may occur relating to masks can be prevented, and children may be more willing to use masks. Increased mask compliance may also indirectly help protect children from the virus.

Keywords: Children, COVID-19, dry eye, mask, ocular surface

Introduction

The use of face masks during the pandemic is one of the most important personal protection methods against the coronavirus disease-2019 (COVID-19) (1,2). Wearing a mask can prevent the spread of virus-containing droplets, and thus it can protect the person (3). Mask use is more effective if it fits well on the wearer's face and shows as little leakage as possible while breathing (3). In children, this situation may gain more importance during the pandemic, especially during the face-to-face education period. However, compared to adults, children may be more reluctant to use masks and may not wear them properly (4). In line with this, we observed that the masks mostly did not fit the face properly in those children who came for eye examinations during the pandemic period. Inappropriate face mask usage in children may have some effects on ocular structures. In the literature, although there were some studies about the effects on the eye of mask usage in adults (5-8), to the best of our knowledge,

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this subject had not been investigated in children until our study. Therefore, we planned this study.

Materials and Methods

This study was carried out with the approval of the University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital's Medical Research Ethical Committee (approval number: 2022/04-10) and in line with the ethical principles of the Declaration of Helsinki. The children and their parents were informed in detail about the study, and risks were explained. Written consent forms were obtained from the participants and their parents.

In the cornea department of our hospital, a total of 58 children aged 9-18 years who had been under follow-up in the pre-pandemic period due to ocular injury in just one eye and who had check-up examinations in the face-to-face education period of the pandemic were initially determined. The ocular data from the non-traumatic (healthy) eyes of 42 cases whose examination findings were fully written up in the file and system records and who met the inclusion criteria were evaluated. The children's age, gender, medical personal history (such as medications, ocular surgery, contact lens usage, ocular and/or systemic diseases), visual acuity, intraocular pressure level, anterior-posterior segment examinations and ocular data [tear film break-up time (TBUT), Schirmer test 1, central corneal thickness, anterior chamber depth, lens thickness and axial length values] were noted from the file and system records. If more than one ocular parameter value had been recorded for the same individual during the pre-pandemic or pandemic period, the average of them was used. If the eye in which the data were evaluated in this study had an acute or chronic ocular disease such as blepharitis, conjunctivitis, keratitis, uveitis, glaucoma and/or a history of ocular trauma or surgery, these eyes were not included in this study. Those children wearing a contact lens for that eye, those individuals having a systemic disease capable of affecting the ocular structures, those cases with a diagnosis of dry eye in the pre-pandemic period, and those children diagnosed with COVID-19 in file and system records were excluded from this study. Those cases who reported wearing a face mask for 2-6 hours a day for at least 3 months in the family and child statements were included in this study.

The best corrected visual acuity of the children was determined with a Snellen chart. Anterior and posterior segment examinations were carried out using a slit-lamp biomicroscope and a 90 D lens. An intraocular pressure measurement was made with a Goldmann applanation tonometer. The TBUT test shows the tear film stability (9,10). In this test, a fluorescein strip (fluorescein paper) is moistened with a saline solution and touched against the lower fornix. Individuals are instructed to keep their eyes open until the first dry spots are observed on the tear film on the cornea illuminated by cobalt blue light under a biomicroscope. The time elapsing between the last blink and the first formation of dry spots is measured. Precorneal tear evaporation is evaluated with this measurement (9,10). The ocular surface staining pattern is also examined at the same time. In the Schirmer test 1 with anesthesia, 0.5% proparacaine HCl is applied, followed by a 5-minute wait. Standard Schirmer test paper is attached to the outer 1/3 of the lower eyelid. The amount of wetting on the paper is noted after 5 minutes. Basal tear secretion is assessed using this test (9,10). Central corneal thickness, anterior chamber depth, lens thickness and axial length was measured using optical biometry device (LenStar LS900, Haag-Streit Diagnostic, Switzerland). The children's ocular data in the pandemic period were compared with the same children's ocular data in the pre-pandemic period.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS Version 20.0) software was used for the statistical analysis. Continuous variables were given as mean ± standard deviation (minimum-maximum) values, while count data was given as case number and percentage. The assumption of normality was tested by the Kolmogorov-Smirnov test. Comparisons were made by the chi-squared test and paired sample t-test. Statistical significance was set at $p<0.05$.

Results

The data of 42 children were evaluated in this study. Eighteen (42.9%) of the cases were female and 24 (57.1%) were male (p=0.523). Their mean age was 14.6±2.1 (9-18) years initially. Fundus examinations of the eyes, in which the data were evaluated in our study, were normal in both the pre-pandemic and pandemic periods. The TBUT values of the children with a mask in the pandemic period were significantly shorter than those of the children without a mask in the pre-pandemic period (9.35±1.40 vs. 12.10±1.05 second, p=0.033). When ocular surface staining was examined, there was no staining in any case in the pre-pandemic period, while a few scattered (minimal) punctate epithelial corneal staining patterns were determined in 4 (9.5%) children in the pandemic period. The Schirmer test 1 value detected in the pandemic period was similar to the value detected in pre-pandemic period (11.14±2.07

vs. 12.03±1.01 mm, p=0.127). Additionally, there were no significant changes in the best corrected visual acuities, central corneal thicknesses, anterior chamber depths, lens thicknesses, and axial lengths between the pre-pandemic and pandemic periods (p>0.05). The clinical findings in the pre-pandemic and pandemic periods are given in Table I.

Discussion

The use of face masks may affect some ocular structures. In the literature, although there have been some studies relating to this subject in healthcare workers and other adult cases (5-8), as far as we know, this subject had not been investigated in children alone to date.

In an online survey administered to medical students, Al-Dolat et al. (11) found no significant association between wearing a face mask and dry eye in the pandemic period. On the other hand, some authors observed an increase in symptoms such as foreign body sensation, light sensitivity, itching, burning and stinging in face mask users (2,12). Additionally, in adults with a previous diagnosis of dry eye, Scalinci et al. (13) reported that the prolonged use of face masks in the pandemic might worsen dry eye symptoms. Nair et al. (14) stated that TBUT was a reliable test to evaluate ocular surface stability in individuals using a face mask. In adults with a previous diagnosis of moderate to severe dry eye, Arriola-Villalobos et al. (7) investigated tear film stability after mask usage. The authors determined that the TBUT value with a mask was significantly shorter than the TBUT value without a mask. They detected that the use of a face mask reduced tear film stability. Similarly, face mask usage was reported to worsen the clinical indicators of ocular surface diseases, such as TBUT and ocular surface staining in adults with dry eye disease (15).

In healthcare workers, TBUT values measured after wearing a mask were shown to be significantly lower than those measured without a mask (5,6). In addition, Esen Baris et al. (6) stated that health-care professionals who wore a face mask for the entire work-day had increased dry eye symptoms. Similarly, in adults, Aksoy and Simsek (8) found that the daily use of a face mask significantly decreased TBUT and increased ocular surface staining.

In our study, the TBUT values of those children with a mask in the pandemic period were significantly shorter than those of children without a mask in the pre-pandemic period. Additionally, we determined minimal punctate epithelial staining pattern in some cases in the pandemic period. We thought that the reason for this significant change in TBUT might be related to increased tear evaporation as a result of the mask. The outermost layer of the tear film is the lipid layer. This layer plays an important role in preventing tear evaporation, and the lipid layer is directly affected by exhaled air (16,17). The temperature of the air inside a face mask was reported to be likely higher than that of the outside air (13). Additionally, air leakage from face masks was shown to be mostly through the gaps at the upper edge of the mask (18). When a face mask does not properly fit on the face, exhaled air may pass through the gaps and move towards the eye (2,5,13,18). This air circulation may

Table I. The clinical findings in the pre-pandemic and pandemic periods

Clinical findings	**Pre-pandemic period (value without a mask) Mean ± SD (range)**	**Pandemic period (value with a mask) Mean ± SD (range)**	**p[a]**
BCVA (Snellen chart/decimal)	0.92±0.07 (0.80-1.00)	0.91±0.08 (0.80-1.00)	0.872
TBUT (second)	12.10±1.05 (11-15)	9.35±1.40 (7-12)	**0.033**
Schirmer test 1 (millimeter)	12.03±1.01 (11-15)	11.14±2.07 (9-14)	0.127
Central corneal thickness (micrometer)	539.07±16.81 (510-572)	538.64±21.35 (506-578)	0.861
Anterior chamber depth (millimeter)	3.53±0.19 (3.28-3.85)	3.54±0.17 (3.32-3.79)	0.792
Lens thickness (millimeter)	3.42±0.29 (3.09±3.78)	3.40±0.36 (3.01-3.92)	0.504
Axial length (millimeter)	22.57±0.28 (22.13-22.89)	22.61±0.36 (22.01-22.99)	0.716

[a]Paired sample t-test, p<0.05 statistically significant.
SD: Standard deviation, BCVA: Best corrected visual acuity, TBUT: Tear film break-up time

accelerate tear evaporation from the ocular surface (2,5,19). Increased tear evaporation may cause ocular irritation and adversely affect ocular surface health (20). In addition, it may increase the risk of ocular surface damage and virus transmission by inducing people to touch their eyes more frequently (20,21). Increased tear evaporation and/or decreased tear secretion were also stated to be among the causes of dry eye (22,23).

In our study, the reasons for the significantly shorter TBUT values in children wearing a mask in the pandemic period may be associated with the above-mentioned mechanisms. In our opinion, another finding which supports these mechanisms may be that taping the upper mask edge has been reported to significantly improve TBUT values (8,14). Sealing the upper edge of the face mask with an adhesive tape was found to significantly decrease air leakage from the face mask (18). Nair et al. (14) detected that taping the upper mask edge resulted in a reduction in dry eye symptoms and a significant increase in TBUT values in healthcare workers. Aksoy and Simsek (8) observed an improvement in TBUT and a significant decrease in ocular surface staining after appropriate taping.

In one study, daily use of a face mask was stated to reduce the Schirmer test values in adults (8). However, Azzam et al. (20) determined that healthcare workers using a mask had normal Schirmer test scores. Similarly, in our study, there was no significant change in the Schirmer test values between the pre-pandemic and pandemic periods. The reason why there was no significant difference in the anesthetized Schirmer test scores in our study may be related to the fact that this test shows the basal tear secretion, not tear evaporation (9,10). We also found no significant changes in the best corrected visual acuities, central corneal thicknesses, anterior chamber depths, lens thicknesses or axial lengths between the pre-pandemic and pandemic periods.

Study Limitations

There were some limitations in our study. The ocular surface disease index questionnaire could not be evaluated in this study. Additionally, daily screen time during the pandemic might have contributed to these results. In the pandemic period, there might be other undetectable causes predisposing to dry eye in children. Another limitation was that this study might have included patients with asymptomatic COVID-19 infection, who were unaware of their condition. Further studies with larger populations may provide more comprehensive data about the effects of mask usage on the ocular surface in children.

Conclusion

In conclusion, to the best of our knowledge, this is the first study to date to evaluate the effects of face mask usage on ocular structures in children alone. The use of face masks may cause increased tear evaporation and dry eye in pediatric cases. Educating children about the correct use of face masks is important. In order to prevent upward airflow, the wire should be shaped appropriately (if bendable nose-wire masks are used) or the upper mask edge should be taped properly. However, it should be ensured that taping does not disrupt lower eyelid function. Regular blink exercises may also be beneficial in protecting the ocular surface. Thus, possible mask related ocular surface changes can be prevented, and children may be more willing to use masks. Increased mask compliance may also indirectly help to protect children from the virus.

Ethics

Ethics Committee Approval: This study was carried out with the approval of the University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital's Medical Research Ethical Committee (approval number: 2022/04-10).

Informed Consent: Written consent forms were obtained from the participants and their parents.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: B.Ö., H.Ö., Design: B.Ö., H.Ö., Data Collection or Processing: H.Ö., Analysis or Interpretation: B.Ö., H.Ö., Writing: B.Ö.

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

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Case Report

A Life-Threatening Complication in a Patient with Ehlers-Danlos Syndrome Musculocontractural Type

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ABSTRACT

Ehlers Danlos syndrome musculocontractural type (mcEDS) is a rare hereditary connective tissue disorder caused by biallelic pathogenic variants in the *CHST14* or dermatan sulfate (DS) epimerase genes resulting in defective DS biosynthesis. It is characterized by congenital malformations and contractures, distinctive facial features and multisystemic fragility-related complications. To date, less than 100 patients with mcEDS have been reported. Vascular complications remain the major morbidity and may lead to mortality in the affected individuals. In this clinical report, we report on a currently 12-year-old boy with a novel homozygous CHST14 variant who presented with typical mcEDS symptoms and subsequently developed a life-threatening subcutaneous skull hematoma following a minor trauma, which required intensive care unit admission and surgical drainage along with several blood transfusions. This case expands the clinical and genetic spectrum of CHST14-related mcEDS which is essential for providing accurate prognosis, management and genetic counseling.

Keywords: EDS, Ehlers-Danlos syndrome musculocontractural type, CHST14, DSE, subcutaneous hematoma

Introduction

Ehlers-Danlos syndrome (EDS) is a genetically and clinically heterogenous connective tissue disorder mainly characterized by joint hypermobility, skin hyperextensibility and generalized connective tissue fragility. According to the revised "Villefranche classification", EDS is classified into 13 subtypes (1). Musculocontractural type EDS (McEDS) was first described clinically as "adducted thumb-clubfoot syndrome" in 1997 by Dündar et al. (2). Since 1997, less than 100 patients have been described (3,4).

Musculocontractural EDS is an autosomal recessive disorder which is caused by pathogenic variants in *CHST14/D4ST1* (carbohydrate sulfotransferase 14/Dermatan-4 sulfotransferase-1, MIM #601776) on chromosome 15q15 or dermatan sulfate epimerase [(DSE), MIM #605942] on chromosome 6q22 (3). Both genes encode enzymes involved in the biosynthesis of DS, a linear polysaccharide which forms DS-proteoglycans by attaching to core proteins and plays a role in cell surfaces and extracellular matrices. DS is an essential component of connective tissue and it is found mainly in skin, blood vessels, cartilage and tendons (4-6). Vascular complications which may sometimes be life threatening may be seen in these patients (7). In this clinical report, we described a mcEDS patient with a novel

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CHST14 variant who was admitted to hospital with massive subcutaneous hematoma after a minor fall complicated with hemorrhagic shock in the clinical course.

Clinical Report

The currently 12-year-old boy of Turkish origin with parental consanguinity was first referred to our center with dysmorphic features and extremity deformities at the age of 12 months. The patient was born to a 28-year-old healthy mother by spontaneous vaginal delivery at 35 weeks of gestation with a birth-weight of 2,400 g. The family history was significant for a younger sibling who was born at 27th gestational week with extremity deformities and passed away 30 minutes after delivery. The patient achieved head control, sat with and without support at 3, 6 and 9 months, respectively. He walked independently by 2 years. He was prone to ecchymosis and hematomas with minor accidents (Figure 1D). At his initial admission, the patient was hypotonic, and a large anterior fontanel, hypertelorism, adduction contracture of thumbs, hypoplastic interphalangeal flexural creases, bilateral talipes equinovarus, and cryptorchidism were noted on physical examination. The patient underwent surgery for talipes equinovarus and cryptorchidism at the ages of 6 months and 2 years, respectively. Ophtalmologic examination was normal. Transfontanelle and abdominal ultrasonography revealed cerebellar vermis hypoplasia and bilateral dilatation of the urinary collecting system, respectively.

Cranial magnetic resonance imaging (MRI) revealed Dandy-Walker malformation (Figure 2, A-C). Echocardiography showed mitral and tricuspid valve prolapse. His serum creatine kinase (CK) level was 643 U/L (normal range: 39-308 U/L). Muscle biopsy at the age of 4 years revealed mild dystrophic and myopathic changes. Dysmorphic features included brachycephaly, broad forehead, hypertelorism, down-slanting palpebral fissures, malar hypoplasia, blue sclera, low set ears, thin lips, and small mouth. He also had short neck and narrow shoulders. Easy bruising, skin hyperextensibility, joint laxity and adducted thumb led to a clinical diagnosis of mcEDS (Figure 1). At the age of 10 years, the patient was admitted to the emergency room with progressive bulging on the right side of his head after a minor trauma. Cranial computed tomography (CT) revealed a massive subgaleal hemorrhage on the occipitoparietal scalp with a 11.5 cm transvers in diameter without a skull fracture (Figure 2D, E). Two days later, follow-up CT image revealed prominent enlargement and upward displacement of the huge subgaleal hematoma

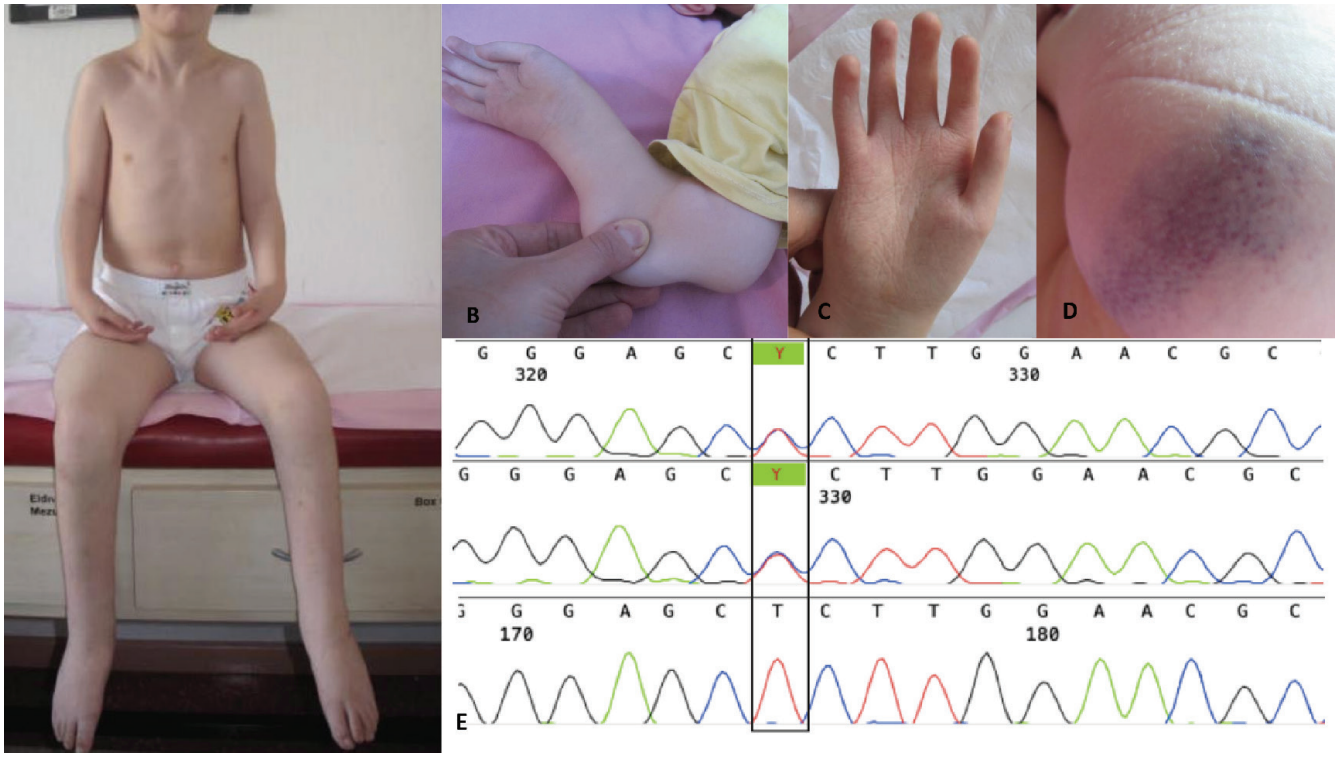

Figure 1. Please note the short neck, narrow shoulders, hypoplastic interphalangeal flexural creases, increased fine palmar creases, thenar and hypothenar atrophy, tapering of fingers and adducted thumb

(Figure 2G). The coagulation parameters were all normal. Scalp necrosis developed as a complication for which he was operated on twice. Necrotic tissue was debrided and a fasciocutaneous flap was applied. During the follow-up, he was admitted to hospital several times due to poor wound healing.

Materials and Methods

The parents' consent was taken for this report. Genomic DNA was extracted from a peripheral blood sample of the patient and his parents using QIAamp DNA Blood Mini Kit (Qiagen Valencia, CA) after informed consent was obtained. WES analysis was performed on the patient using an Ion Ampliseq Exome RDY kit and Ion Proton sequencer. Sanger sequencing on the patient and his unaffected parents was performed. Exon 1, which is the only coding exon of *CHST14*, was sequenced with exonic-intronic boundary using BigDye Terminator on an ABI 3500 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA).

Exome Sequencing

Exome sequencing (ES) was carried out using an SeqCap EZ Exome+UTR Library and TruSeq Version 2 sequencing instruments. Exome data were analyzed using Varsifter uins, an exome-based targeted panel approach, to identify variants in known neuromuscular and *EDS* genes. Pathogenicity was assessed using the American College of Medical Genetics and Genomics (ACMG)/Association for Molecular Pathology guidelines for the interpretation of sequence variants, which includes population data, computational and predictive data using various lines of computational evidence (CADD, Polyphen, Sift) and segregation data.

Results

ES analysis revealed a novel homozygous missense variant in exon 1 of *CHST14* (NM_130468.8: c.644C>T, p.Pro215Leu) and this was confirmed by Sanger sequencing. Both parents were heterozygous (Figure 1). The pathogenicity of the identified variant was assessed using online prediction tools including CADD scores (https://cadd.gs.washington.edu/),PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/), MutationTaster (http://www.mutationtaster.org), and SIFT (https://sift.bii.a-star.edu.sg/sift4g/SIFT4G_codes.html). The CADD score (GRCh37-v1.6) was calculated to be 32 (deleterious). The variant is classified as "likely pathogenic" according to ACMG 2015 (PM1, PM2, PP2, PP3), "probably damaging" according to Polyphen-2, "damaging" according to SIFT,

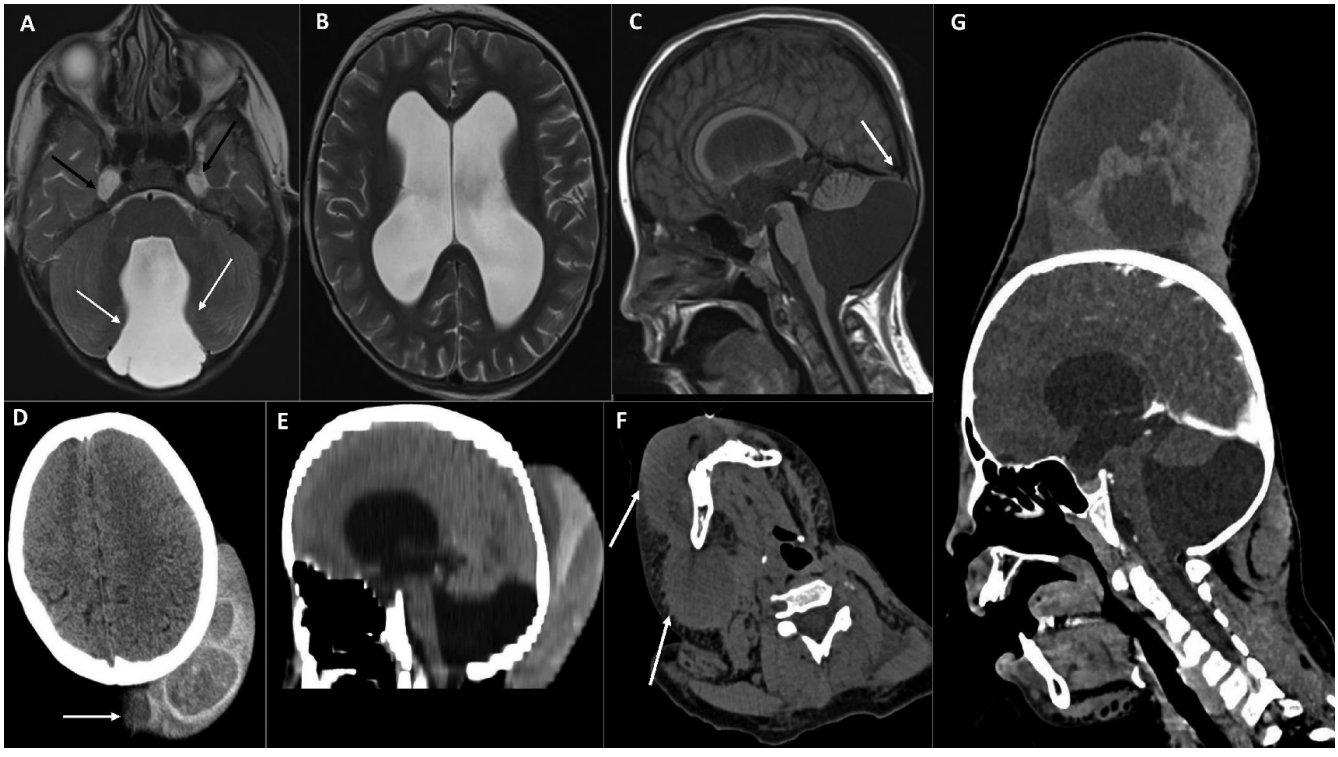

Figure 2. Cranial MR (A-C) obtained 7 years before trauma and CT imaging (D-G) obtained at the period of trauma. CT image reveals an acute subgaleal hematoma on the left parieto-occipital region with a 11.5 cm transvers in diameter without skull fracture (D)

MR: Magnetic resonance, CT: Computed tomography

and "disease causing" according to Mutation Tester. The variant is absent in the gnomAD browser.

Discussion

In this clinical report we described a patient harboring a novel homozygous *CHST14* variant, p.Pro215Leu, who experienced a life-threatening vascular complication requiring PICU admission.

Characteristic facial features of mcEDS include hypertelorism, short and down-slanting palpebral fissures, blue sclerae, thin upper lip vermilion, small mouth, low-set and rotated ears, and high palate, all of which were present in our patient. Characteristic cutaneous findings such as skin hyperextensibility, easy bruisability, skin fragility with atrophic scars and increased palmar wrinkling along with various skeletal findings including adduction-flexion contractures, talipes equinovarus, scoliosis, pectus deformity and joint dislocation were also present in our patient. In the follow-up, he experienced joint pain as well as hyperalgesia to pressure, which is not a common finding among these patients.

Although intellectual disability is not common in mcEDS, motor developmental delay is frequently reported due to muscle weakness. Decreased fetal movements, severe hypotonia at birth, inability to suck, and swallowing difficulties are also frequently reported (3). In addition, patients are usually evaluated for myopathic diseases with muscle biopsy and EMG as was the case with the present patient. Our patient had thenar and hypothenar atrophy and a high serum CK level at the age of 4 years without clinically progressive weakness. Voermans et al. (8) reported a patient with generalized muscle hypotonia, a mildly elevated CK level and hypoplasia of the intrinsic hand muscles in whom muscle biopsy and EMG revealed myopathic involvement. Various central nervous system abnormalities including ventricular dilatation, cerebral and cerebellar atrophy, short corpus callosum, absence of septum pellucidum, spinal cord tethering, gray matter heterotopias, cortical dysplasia, hypoplasia of hippocampi, septo-optic dysplasia, and Dandy-Walker malformation are reported in mcEDS patients (3,4). Cranial MRI revealed Dandy-Walker malformation in our patient as well.

Vascular complications such as hematomas, arterial dissections and aneurysms, intracranial hemorrhage, gastrointestinal bleeding, perioperative hemorrhage, and prolonged menstrual bleeding can be seen in EDS patients. Large subcutaneous hematomas are also reported after minor traumas or even spontaneously in patients with mcEDS (7). Large subcutaneous hematomas were previously reported in 46 out of 58 (79%) mcEDS patients (3). No major coagulation abnormality is observed in mcEDS patients as was the case in our patient (5). Tendency to massive bleeding in mcEDS is generally explained by vascular abnormalities leading to vascular fragility which is thought to be caused mainly by a lack of DS (6,7).

DS, an important glycosaminoglycan necessary for fetal development, forms side chain of decorin which is an essential proteoglycan in connective tissues. It connects collagen fibrils, plays a role in the cell surface and plays role in matrix assembly and cell differentiation (9,10). It was observed that in the skin fibroblast samples of mcEDS patients, DS disaccharides on decorin was absent, while chondroitin sulfate (CS) was abundant (2,5,10). This imbalance between CS and DS is thought to be responsible for multi-systemic findings affecting various organ systems in early development (5,9,10). In *DSE*-mcEDS patients, clinical findings are milder because, although DS is absent on decorin in *CHST14*-mcEDS, small fractions are found in DSE-mcEDS. Also, it is thought to be compensated by *DSE2* enzyme (9,10). No genotype-phenotype correlation has been established in *CHST14*-mcEDS patients so far (3,9).

The missense variant reported in this study, c.644C>T; p.Pro215Leu, is located in a highly evolutionary conserved region in the sulfotransferase domain. The change of proline, a ring shaped amino acid, to leucine, a branched-chain amino acid, is thought to disrupt the protein structure. Another *CHST14* variant, p.Arg213Pro, located near the region of the variant detected in the present study was reported previously by Dündar et al. (2) and Janecke et al. (5). Janecke et al. (5) demonstrated a 50% reduction in levels of *CHST14* mRNA, decreased amounts of DS, reduced 4-sulfation and increased 6-sulfation in fibroblasts. New short D4ST1 species were demonstrated in cells expressing p.Arg213Pro, that arise as a result of proteolytic cleavage and different intracellular processing in these cells from wild type cells. Trace amount of D4ST1 which was thought to be due to premature degradation of new species before reaching golgi was found in transfected cells with this missense variant (2).

In conclusion, mcEDS is one of the hereditary connective tissue and muscle overlap disorders with a recognizable phenotype, yet with a challenging diagnosis on some occasions. The fragility of connective tissue renders patients susceptible for potentially life-threatening vascular complications requiring multidisciplinary care. Caution

must be taken and adequate supportive therapy should be provided accordingly.

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Ethics

Informed Consent: Written informed consent was obtained from the patient's parents.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.D., P.Ö.Ş.K., R.G., G.E.U., K.B., G.H., Concept: T.D., P.Ö.Ş.K., Design: T.D., P.Ö.Ş.K., G.H., Data Collection or Processing: T.D., P.Ö.Ş.K., R.G., Analysis or Interpretation: S.D., R.G., C.B., Literature Search: T.D., P.Ö.Ş.K., G.H., Writing: T.D., P.Ö.Ş.K.

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Case Report

Severe Extremity Anomaly and Neurodevelopmental Retardation in an Infant with TAR Syndrome and Differential Diagnosis in Radial Defects

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ABSTRACT

Thrombocytopenia-absent radius (TAR) syndrome is a rare congenital syndrome in which thrombocytopenia and the absence of radius can be accompanied by various organ anomalies. Bilateral phocomelia is the most severe form in this clinic. Thumbs are always present. The deletion of the *RNA-binding motif protein 8A* (*RBM8A*) gene on chromosome 1q21.1 in Array Comparative Genomic Hybridization confirms the diagnosis of TAR syndrome. Thrombocytopenia, which can cause complications, tends to resolve in the first year of life. Although there are delays in motor development, mental retardation is not one of the common clinical findings of this syndrome. In the differential diagnosis of severe radial defects, TAR syndrome, Holt-Oram syndrome, Roberts syndrome, Fanconi anemia, and VACTERL association are included. The presence of key findings of each syndrome is important in the differential diagnosis. Here, we aimed to evaluate the approach to the differential diagnosis of severe radial anomalies in a patient with TAR syndrome and neuromotor retardation.

Keywords: Phocomelia, TAR syndrome, RBM8A, 1q21.1

Introduction

Thrombocytopenia-absent radius (TAR) syndrome (OMIM 274000) is a rare congenital disorder with an estimated prevalence of 1 in 100,000 to 1 in 200,000 births. The cardinal manifestation of TAR syndrome was described by Hall et al. (1) in 1969. It is characterized by thrombocytopenia and bilateral absence of the radii with preservation of both thumbs. However, many additional features, including other skeletal anomalies, heart defects, genitourinary system anomalies, and cow milk intolerance have been reported (2).

Phocomelia, which is defined as the absence of the radius, ulna and humerus and affect function, constitute the most a severe form of the clinic. Depending on the extent of the upper extremity function, delays in motor developmental stages may be seen in patients, but neuromotor retardation is not a typical finding of this syndrome. In the differential diagnosis of severe radial defects, which can also be detected by fetal ultrasonography (US) in the prenatal period, TAR syndrome, Holt-Oram syndrome, Roberts syndrome, Fanconi anemia and the VACTERL association are included. Finding the key differential findings of each syndrome is important in diagnosis. In this report, we aimed to report on a female infant with TAR syndrome accompanied with severe upper limb phocomelia with neurodevelopmental retardation and to discuss the differential diagnosis of radial anomalies.

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Case Presentation

A 16-day-old female with bilateral upper limb phocomelia was referred to our Pediatric Genetics Department. The patient was the first child of non-consanguineous parents. Family history was normal. The mother was a non-smoker with no history of exposure to teratogenic agents. Routine US performed at 13 weeks of gestation showed bilateral absence of the arm and forearm with both hands being normal. The parent refused to do amniocentesis for fetal karyotyping. She was born at 39 weeks of gestation via cesarean section with APGAR score of 9/10 at 1 and 5 minutes, respectively. At birth, a weight of 2,750 g (-1.32 SDS), a length of 48 cm (-0.66 SDS) and an occipitofrontal head circumference of 34 cm (-0.36 SDS) were measured. Physical examination revealed bilateral upper limb phocomelia with no thumb deformity, radial club hand, splenomegaly, micrognathia, low-set ear, and 5th finger clinodactyly (Figure 1). No abnormality of the lower extremities was noted except for a placement anomaly on the 4th toes of the feet. Laboratory values included a white blood cell measurement of (WBC) 42×10^{9}/L, hemoglobin of 9 g/dL, and a platelet count of 11×10^{9}/L. Peripheral blood smear showed increased myelocytic activity, thrombocytopenia, and neutrophilia. Bone marrow aspiration biopsy was normocellular with undetected megakaryocytes. Additionally, there was no malignant infiltration. Immunological parameters revealed low levels of immunoglobulins and cow milk intolerance. Skeletal X-ray imaging confirmed the bilateral absence of humeri, radii, ulnae, and clavicles with hook like appearance. There was no vertebra or costal anomalies (Figure 2). Transthoracic echocardiography revealed a small ventricular septal defect (VSD). There was no clinical evidence of renal abnormality on the abdominal US. A normal female karyotype (46, XX) was found on chromosomal analysis. On array-CGH, a pathogenic interstitial heterozygous deletion of 562 kb on chromosome 1q21.1 including the *RNA binding motif protein 8A* (*RBM8A*) was detected.

Figure 1. Proband showing bilateral absence of the arm and forearm, arm/shoulder muscle hypoplasia with both hands normal, no thumb deformity, low-set ears, and micrognathia

Bilateral strabismus was noticed at the age of 6 months and she had an operation due to strabismus. An examination at the 20th month revealed that she was unable to sit or walk unassisted. When the psychometric analysis was performed, retardation was observed in motor, adaptive, cognitive, and language development. Cranial MR imaging was normal. At her last examination, her body weight was measured as 7.6 kg (-2.6 SDS), her height was 65 cm (-5 SDS), and her head circumference was 43 cm (-3.1 SDS). She is under follow-up for intermittent screening for thrombocytopenia and her last platelet count was 137×10^{9}/L.

Discussion

TAR syndrome is a rare genetic disorder associated with thrombocytopenia and bilateral absence of radii. It

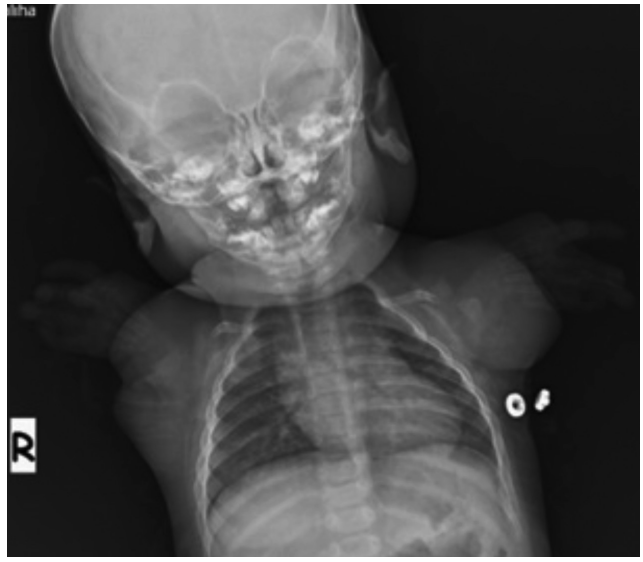

Figure 2. Anteroposterior chest image showing bilateral absence of radius, ulna, and humerus, clavicles with hook-like appearance, no vertebral and costal anomalies

has also been found to be associated with genitourinary malformations (duplicated ureter, horseshoe kidney, renal dysgenesis, agenesis of the uterus, cervix, and the upper part of the vagina), cardiac anomalies (mainly septal defects), dysmorphic features (tall forehead, small chin, low-set ears), and often cow's milk intolerance (2,3). All patients with TAR syndrome have a bilateral absence of the radii, and the thumbs are always present even if they are hypoplastic. The severity of radial anomalies varies from hypoplasia of the radius to phocomelia. In a study including 30 patients, phocomelia was present in 33% of all cases (4). Greenhalgh et al. (2) and Houeijeh et al. (5) found the rate of phocomelia to be 28% and 11%, respectively in their case series with TAR syndrome. Lower limb malformations are often observed, which include hip dysplasia, knee abnormalities, and shortening of the long bones (4). However, upper limb abnormalities tend to be more severe. Our patient had phocomelia, which is the most severe form of upper extremity abnormalities. No major lower extremity abnormality was seen in our case.

The genetic inheritance pattern of TAR syndrome is uncertain, however, a study by Klopocki et al. (4) identified a minimal common interstitial microdeletion of 200-kb on chromosome 1q21.1. This microdeletion in the long (q) arm of chromosome 1 usually involves the deletion of a gene called the *RBM8A* gene. In several cases, it is inherited from an unaffected parent, while in others, it originates de novo and the presence of a 1q21.1 microdeletion is necessary but not sufficient to cause this phenotype. In our study, we could not determine genetic inheritance as the parents declined to undergo genetic testing. Prenatal diagnosis of TAR syndrome is also feasible (6). Radial abnormality can be detected in the early weeks of gestation by the fetal US. The confirmation via molecular genetic testing to detect the deletion in the 1q21.1 allows for the prenatal diagnosis of TAR syndrome.

The exact pathophysiology of thrombocytopenia is still unclear in TAR syndrome. The supposed reason for the low platelet count is the paucity of megakaryocytes. In the first months of life, patients may have severe thrombocytopenia ($<30\times10^9$/L), complications such as bleeding, petechiae, and associated mortality may be high (7). The main concern for patients with TAR syndrome is the risk of life-threatening bleeding, however, thrombocytopenia of unknown cause in the neonatal period typically resolves in the first year of life (7). It can also fluctuate over time. Thus, serial platelet count monitoring has been recommended. Our case had petechiae in the neonatal period and received a platelet transfusion due to her low platelet count. No complications secondary to thrombocytopenia were observed in her clinic, and platelet values started to increase from the third month in line with the literature.

Motor developmental delay can be seen in cases with TAR syndrome due to skeletal system anomalies. However, there are a few studies that report that mental retardation may be present in 7% of patients due to intracranial hemorrhages secondary to thrombocytopenia and that central nervous system pathologies (cerebral, cerebellar anomalies, vascular malformations, epilepsy, etc.) maybe associated with this condition (8-10). There is a study showing that the *RBM8A* gene has a critical role in the regulation of cortical progenitor cells and neurodevelopment (11). The neurodevelopmental retardation of our patient despite her normal MR imaging can be explained by the loss of the regulatory role of the *RBM8A* gene, which is deleted in TAR syndrome, in brain development.

In a study consisting of 20 cases diagnosed with 1q21.1 microdeletion syndrome, 55% had eye anomalies (congenital cataract, strabismus, coloboma, hyperopia, Duane anomaly), and strabismus was observed in 20% of these cases (12). There is little literature on ocular manifestations of TAR syndrome. As an interesting finding, a newborn case in which TAR syndrome was accompanied by bilateral congenital cataracts was reported (13). Our patient had a history of surgery when she was 6 months old due to bilateral strabismus. For this reason, it is important to evaluate the eye examination in detail and to make an early diagnosis of this syndrome. We also hope to contribute to the literature due to the severe strabismus in our case.

TAR syndrome needs to be differentiated from other syndromes which contain radial anomalies such as thalidomide embryopathy, Holt-Oram syndrome, Roberts syndrome, Fanconi anemia, and VACTERL associations. The possible diseases in the differential diagnosis of TAR syndrome are summarized in Table I. The questioning of any possible drug use in the mother's pregnancy can be used to exclude thalidomide embryopathy. Holt-Oram syndrome is associated with upper limb malformations with cardiac abnormalities (atrial septal defect and VSD) (14). Abnormalities of the metacarpals and carpal bones can be seen and the thumbs are usually absent or severely hypoplastic. Roberts syndrome is characterized by severe growth retardation, limb defects, and craniofacial anomalies, and patients may occasionally exhibit normal thumbs (15). Fanconi anemia is caused by a defect in DNA repair, bone marrow suppression, thumb and/or radial

Table I. Differential diagnosis of severe radial anomalies

Condition	Inheritance pattern	Genetic impairment	Upper limb abnormality	Hematologic disorder	Other clinical features
TAR syndrome	AR*	Microdeletion on chromosome 1q21.1	Bilateral absence of the radii with the presence of both thumbs	Hypo-amegakaryocytic thrombocytopenia	Lower limb malformations, cardiac anomalies, genitourinary malformations, dysmorphic features, cow's milk intolerance
Holt-Oram syndrome	AD*	Mutation in TBX5	Thumb anomalies most common and the thumbs are usually absent or malformed.	None	Congenital cardiac defects
Roberts syndrome	AR	Mutation in ESCO2	Symmetric reduction in the number of digits, and length or presence of bones. (Thumb aplasia or hypoplasia, phocomelia, olygodactyly, radial, ulnar and humeral aplasia, tetraphocomelia)	None	Craniofacial anomalies, pre- and postnatal growth retardation
Fanconi anemia	AD, AR, X-linked	Defect in DNA repair, different genes can cause	Thumb and/or radial hypoplasia	Bone marrow suppression, pancytopenia and a high risk of developing acute myeloid leukemia	Skin pigmentation, short stature, gastrointestinal tract and genitourinary abnormalities
VACTERL association **V**ertebral **A**nal **C**ardiac **T**racheoesophageal fistula/ **E**sophageal atresia **R**enal anomalies **L**imb anomalies	Isolated	Sporadic	Thumb and/or radial hypoplasia/aplasia, radioulnar synostosis, polydactyly, syndactyly Triphalangeal thumb presence	None	Growth deficiency Spinal and cranial abnormalities

*AD: Autosomal dominant, *AR: Autosomal recessive

deformities, and a predisposition to cancer is often present (16). In VACTERL association, the diagnosis is considered in the presence of at least three of the vertebral, anal, cardiac, renal anomalies, and tracheoesophageal fistula/ esophageal atresia. Thumb aplasia/hypoplasia, radius anomalies, polydactyly, syndactyly, and lower extremity anomalies can also be seen with varying severity (17). In our patient, the key points that distinguish TAR syndrome from the other syndromes are radial abnormalities and the presence of both thumbs. Additionally, thrombocytopenia is mandatory to differentiate TAR syndrome from other diagnoses. Nevertheless, genetic tests should be used to confirm the clinical diagnosis.

Conclusion

TAR syndrome is a rare syndrome characterized by bilateral absence of the radii with the presence of both thumbs and thrombocytopenia. Clinical features together with the detection of the 1q21.1 deletion allow clinicians to conclude from the aforementioned differential diagnoses that TAR syndrome is most likely. The risk of bleeding is high during the first year of life. Thrombocytopenia is generally fluctuant in nature, but it is usually transient. Serial monitoring of the platelet count is essential in the management of patients. Patients can have many additional abnormalities, including skeletal, urogenital, and heart defects. Cranial Imaging is recommended in cases with neuromotor retardation. Therefore, patients with TAR syndrome should be assessed for other associated malformations. Orthopedic interventions may be needed to maximize limb function.

Ethics

Informed Consent: Permission was obtained from the patient's parents to share their medical information.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.K., N.Ö., B.N., Gü.K., E.M., Design: G.K., B.N., Literature Search: G.K., N.Ö., B.N., Gü.K., E.M., Writing: G.K. B.N. E.M.

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Case Report

Virilizing Adrenocortical Carcinoma Oncocytic Variant in a Child with Heterosexual Precocious Puberty and a Literature Review

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ABSTRACT

Androgen-secreting adrenal tumors are aggressive cancers in childhood; however, they are rare in clinical practice. Children with adrenal carcinoma usually present with peripheral precocious puberty, premature pubarche, signs of virilization and clitoromegaly. We present a case of 4 year-old girl with premature pubarche, clitoromegaly and bone age advancement, who was subsequently diagnosed with pure androgen-secreting oncocytic adrenal carcinoma. After the removal of the adrenal tumor, our patient developed precocious puberty. In patients with functioning adrenocortical carcinoma who have had surgical removal, clinical follow-up and hormonal marker examination for the secondary effects of excessive hormone secretion at least every 2 or 3 months may be a useful option after surgery. The aim of this article is to emphasize that adrenal tumors can be seen in patients presenting with virilization findings. We also present a literature review of these tumors, which are very rare in childhood.

Keywords: Oncocytic variant adrenocortical cancer, peripheral precocious puberty, clitoromegaly

Introduction

Adrenocortical carcinoma (ACC) is an endocrine neoplasm arising in the outer part of the adrenal gland. Although most cases of ACC are sporadic, they have an association with hereditary cancer syndromes such as Li-Fraumeni syndrome and Beckwith-Wiedemann syndrome (1,2). They are categorized as functional (hormone-secreting), which are most commonly found in children and adolescents, or non-functional (silent), which are usually found in adults with symptoms of abdominal discomfort or back pain caused by the large mass of the tumor (3,4). ACC has a bimodal distribution; the first peak is in children less than five years and the second around the fifth decade (5). It comprises 0.3-0.5% of neoplasms detected in patients under the age of 15. ACC can be benign or malignant. The most common clinical presentation of ACC in children is peripheral puberty precocious observed in approximately 50-84.2% of cases and Cushing's syndrome in the remaining patients (6,7). Pure androgen-secreting adrenal tumors (PASATs) are rare in clinical practice (1). The majority of cases present with a combination of clinical features of Cushing's syndrome and hyperandrogenism. Oncocytic adrenocortical

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tumor is a rare subtype which represents approximately 10% of adrenocortical tumors with a challenging diagnosis and histo-prognostic assessment. It is usually accepted that oncocytic adrenocortical tumors have a more moderate clinical behavior than conventional adrenocortical tumors. Here, we describe the rare case of a 4-year-old girl with pure androgen secreting adrenal oncocytic carcinoma who presented with premature pubarche, clitoromegaly and advanced bone maturation. In this article, we also aimed to review the literature on functional adrenocortical cancers in childhood.

Case Report

A 4-year-old girl presented with a complaint of pubic hair development which had been ongoing for about one month. She had no history of axillary hair growth or thelarche. She was born at full-term without any perinatal problems and had no history of previous hospitalizations. Her parents were not related. On physical examination, her body weight was 21 kg [1.17 standard deviation (SD)], height was 111.5 cm (0.94 SD) and body mass index was 0.93 kg/m^2. The target height was 157.7 cm (-0.91 SD) which was 1.8 SD below her current height SD. Her blood pressure was 100/70 mmHg. Pubertal examination revealed no breast development or axillary hair; however, pubic hair was compatible with Tanner stage 3. She had an enlarged clitoris, 20 mm in length, with a normal vaginal opening (Figure 1). Clitoromegaly had not been recognized by her parents before and there were no other signs of genital ambiguity, systemic disease or Cushing syndrome. Abdominal examination revealed no palpable mass.

Laboratory investigations indicated hyperandrogenemia; serum total testosterone 206 ng/dL (<10 ng/dL), Dehydroepiandrosterone sulfate (DHEA-S) 447 mcg/dL (9-42 mcg/dL) and pre-pubertal gonadotropin levels follicle-stimulating hormone 0.8 U/L (0.4-3U/L), luteinizing hormone (LH) 0.2 U/L (<0.1U/L) and Estradiol <20 pg/mL (<16 pg/mL). Table I shows the laboratory values of our patient before and after the operation. Her bone age was seven years and ten months according to the Greulich & Pyle method. A standard dose adrenocorticotropic hormone test was performed in order to rule out classic or late-onset congenital adrenal hyperplasia and it was normal. An abdominal ultrasound showed a 22 mm by 31 mm well-defined and hypoechoic solid lesion in the right adrenal gland. Abdominal magnetic resonance confirmed a mass with a smooth contour that did not contain significant fat (Figure 2).

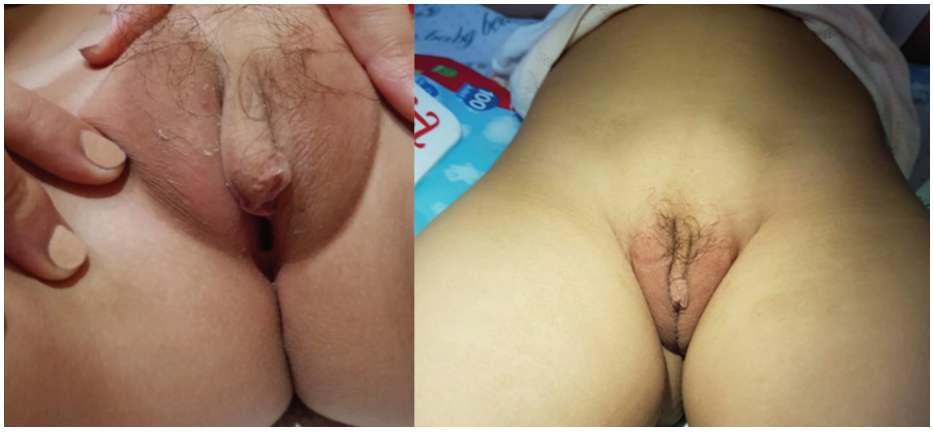

Figure 1. The appearance of the patient's external genitalia: cliteromegaly and vaginal opening

Table I. Pre-and post-operative hormone levels of the patient

	Pre-operative	Post-operative	Normal range
Total testosterone (ng/dL)	206	<10	(<10)
DHEA-S (mcg/L)	447	8.4	(<9-42)
FSH (U/L)	0.8	7.47	(0.4-3)
LH (U/L)	0.2	1.04	(<0.1)
Estradiol (pg/mL)	<20	25.25	(<16)
Cortisole (08:00 a.m.) (µg/dL)	9.95	13	(5-21)

The patient was diagnosed with an androgen secreting adrenocortical tumor based on the clinical, biochemical, and radiological investigations. Although she had no signs of Cushing's syndrome, hypertension or electrolyte abnormalities, further hormonal analyses were performed to identify any accompanying cortisol or aldosterone excess. An over-night dexamethasone suppression test revealed normal suppression at the cortisol level. Plasma renin activity and aldosterone levels were also in the normal ranges. The patient underwent right open adrenalectomy. The resected mass was a well encapsulated tumor of dimensions 4x3.2x1.3 cm.

Histopathological examination revealed oncocytic variant ACC (Figure 3). A metastatic work-up including chest computed tomography (CT) and positron emission tomography (PET)-CT scans revealed negative findings. The patient's tumor was stage 1. The patient was evaluated by the pediatric oncology council. Rigorous follow-up was decided upon without further postoperative chemoradiotherapy based on the borderline pathological classification criteria and no evidence for metastatic. After the operation, her total testosterone and DHEA-S values returned to normal levels. However, serum LH level increased to pubertal values. The patient developed central precocious puberty due to hypothalamic-pituitary-ovarian activation following the surgical removal of the androgen-producing tumor. The gonadotropin-releasing hormone agonist (leuprolide acetate) was started at 3.75 mg every 28 days.

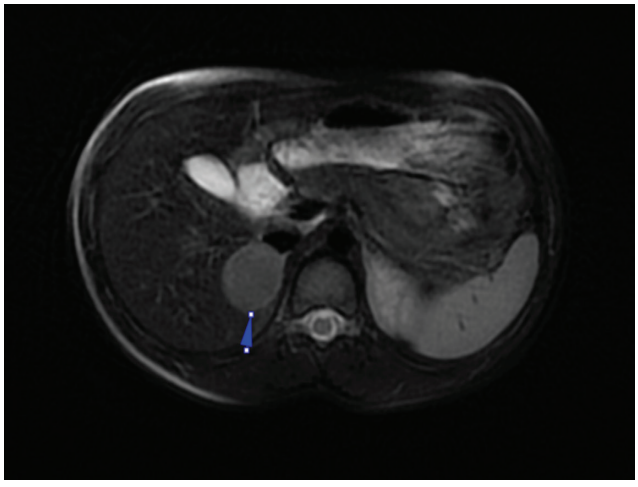

Figure 2. Abdominal MRI of the patient
MRI: Magnetic resonance imaging

Discussion

ACC is diagnosed at a frequency of 0.3 to 0.4 per million children annually (6-8). Pediatric ACCs are more commonly diagnosed in early childhood (<4 years) and predominantly affect girls (9). ACC can arise as either a non-functional or functional tumor. Non-functional ACC is most common in adults, whereas more than 90% of childhood ACCs are functional (10). Virilization alone or signs of other adrenal hormone overproduction are the most common endocrine presentation in pediatric patients (11). Isolated Cushing's syndrome, the primary symptom of adult ACC, is extremely rare, as is Conn's syndrome. Most cases of pediatric ACC are initially diagnosed based on their clinical and biochemical laboratory findings. Hagemann et al. (11) reported that approximately 90% of pediatric ACCs are hormonally active and the type of hormone secretion can lead to varied clinical presentations. In a large cohort of children with ACC, more than 90% of young children had virilizing features. In contrast, there was a tendency toward Cushing's syndrome and non-functional tumors

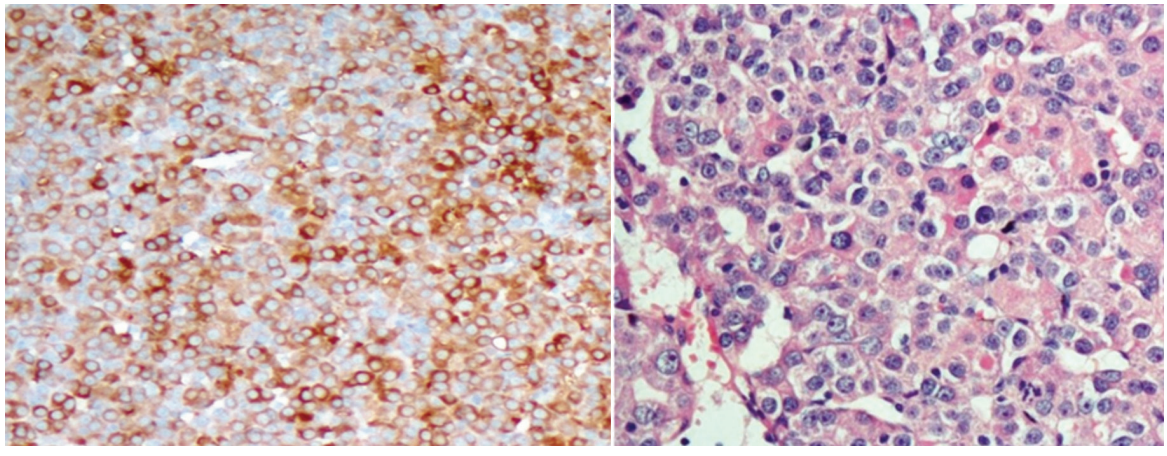

Figure 3. Microscopic findings of the oncocytic variant adrenocortical tumor

in adolescents (6). Our patient had a PASAT, which is extremely rare. In 2017, Tong et al. (12) reported 9 patients with PASATs, whose ages ranged between 3.5 and 64 years. Kamilaris et al. (13) reported two further girls aged 15 and 12 years of age with PASATs that predominantly secreted testosterone (14). These patients presented with primary amenorrhea and virilization. As illustrated by our case, signs of androgen hypersecretion can include accelerated growth velocity, bone age advancement, clitoromegaly, and premature pubarche. Michalkiewicz et al. (5) also pointed out that these children often do not appear to be ill and in fact their accelerated growth in the early stages can initially be mistaken as a sign of good health.

The diagnostic criteria for oncocytic ACC are different from those for conventional ACC. Oncocytomas are a rare etiology of the adrenal mass and they are defined as neoplasms consisting of cells with an abundant amount of eosinophilic granular cytoplasm packed with swollen mitochondria and composed solely or primarily of oncocytes (15). By definition, these tumors are made up of at least 50% oncocytic cells and are either mixed (50-90% oncocytic cells) or pure (>90%). The diagnostic criteria for oncocytic ACC are different from those for conventional ACCs. Identification of the oncocytic character of tumor cells is the first diagnostic difficulty. Prognostic evaluation of these tumors is the second difficulty given the multiplicity of scoring systems and the risk of overestimating potential malignancy, such as with the Weiss score, owing to parameters that are intrinsic to oncocytic cells (eosinophilic character, elevated Fuhrman grade, usually diffuse architectural structure, a minimum Weiss score of 3). The Lin-Weiss-Bisceglia (LWB) score, specifically developed for this type of tumor (16), has been the most commonly used since the publication of the Wong et al. (16) study and was recently recommended by the World Health Organization in 2017 LWB system: (1) major criteria (a mitotic rate of more than 5 mitoses per 50 high-power fields, any atypical mitoses or venous invasion), (2) minor criteria [large size (>10 cm and/or >200 gr), necrosis, capsular invasion or sinusoidal invasion] and (3) definitional criteria (predominantly cells with eosinophilic-granular cytoplasm, high nuclear grade and diffuse architectural pattern). It is often challenging to differentiate benign from malignant adrenocortical oncocytic carcinoma. Most studies demonstrated that a combination of clinical, biochemical and, in particular, histological features can distinguish adenoma from carcinoma. The presence of fibrous encapsulation in contrast imagining is suggestive of oncocytoma. According to the LWB system, our patient had 2 of the major criteria (atypical mitosis and a mitosis rate of more than 5 mitoses) and 2 of the minor criteria (capsule invasion, sinusoidal invasion) used for oncocytic tumors.

Metastatic work-up included a chest CT scan and a PET-CT scan, which revealed negative findings. Our patient's stage was 1. Based on the borderline criteria of the pathologic classification and no metastatic evidence, we decided just to observe her without further post-operative chemoradiotherapy.

Oncocytic ACCs are uncommon and their incidence is not precise. In the current literature, one hundred and fifty cases have been reported which were most often single cases or small series. The most extensive study consisted of 43 patients (15) with an average age of 47.5 years (38 between 55.8). Of these tumors, 28 were reported to be pure oncocytic tumors (>90% oncocyte), while 15 were mixed tumors (50-90% oncocyte with standard adrenal tumor cell components).

Oncocytic ACCs are rare in adults and they are even rarer in children. Oncocytic adrenocortical tumors are rare, with few cases reported in the literature. No more than 20 cases in children have been reported (17). A literature review of adrenocortical cancer is given below (Table II).

In a Turkish study published in 2017, 3 patients were diagnosed with oncocytic ACC between 2011-2016 (18).

In 2020, Akın et al. (19) reported on a children who had an oncocytic ACC and rhabdomyosarcoma at the same time. The patient was an 18-month-old boy and he was admitted with virilization of the genital area, penis enlargement and erection which had begun six months prior. Serum total testosterone, androstenedion, and DHEAS were measured in higher than normal ranges. A right adrenal mass was detected. After adrenalectomy, histopathological examination revealed oncocytic ACC.

Our patient had functional ACC which synthesized androgens only and presented with virilization findings. We made this case report to draw attention to this very rare disease.

Conclusion

In conclusion, virilization is an important manifestation of adrenocortical tumors in both sexes. We report the case of virilizing functional oncocytic ACC in a girl with accelerated skeletal maturation, clitoromegaly and premature pubarche. A high index of suspicion and an

Table II. Cases of oncocytic adrenocortical tumor in children reported in the literature

Ref.	Age in year	G	Clinical features	Size	Treatment	Follow-up	Prognosis
Gumy-Pause et al. (20)	12	F	Fatigue, headache, acne vulgaris, and abdominal pain	5.0 cm × 4.3 cm × 2.2 cm	Open adrenalectomy	Normal hormone levels 18 month after diagnosis	No recurrence
Lim et al. (21)	14	F	Deepening of the voice and excessive hair	17.5 cm × 15 cm × 14 cm	Open adrenalectomy	Normal hormone levels 2 week after operative resection	No recurrence
Tahar et al. (22)	6	F	Precocious puberty	3.0 cm × 2.0 cm × 1.5 cm	Open adrenalectomy	Twelve month after operative resection, he manifestations of pseudoprecocious puberty were effectively reduced	No recurrence
Subbiah et al. (23)	31/2	F	Premature pubarche, clitoromegaly	2.5 cm x 2 cm	Open adrenalectomy	Normal hormone levels 1 month after operative resection	No recurrence
Kawahara et al. (24)	11	F	Fever, weight loss, increased inflammatory markers	4.5 cm x 4.5 cm x 2.5 cm	Open adrenalectomy	The inflammatory markers and IL-6 levels normalized within 2 week after tumor resection	No recurrence
Yoon et al. (25)	10	F	Precocious puberty	6 cm x 4 cm	Open adrenalectomy	One year after surgery without new lesions	No recurrence
Akin et al. (26)	11	M	Metabolic, alkalosis, polyuria, polydipsia, hypokalemia	4.5 cm x 2.5 cm x 2.5 cm	Laparoscopic surgery	After the operation, the patient's polyuria and hypokalemia resolved, and his aldosterone level returned to normal	No recurrence
Ranganathan et al. (27)	5	M	Precocious puberty, acne	4.2 cm × 3.9 cm × 2.6 cm	Laparoscopic surgery	Three month later, the patient had lost 3.2 kg and had grown 3.5 cm. Clinically, his symptoms resolved with no progression of pubic hair, axillary hair, or acne	No recurrence
Mardi (28)	14	F	Hirsuitism	18 cm × 8.0 cm × 7.0 cm	Open adrenalectomy	The hirsuitism resolved gradually following surgery	No recurrence
Chen et al. (29)	15	M	Lower back pain	9 cm x 6.3 cm	Laparoscopic surgery	Lower back pain relief	No recurrence
Yordanova et al. (30)	9	F	Virilization	2.2 cm x 2.2 cm	Laparoscopic surgery	Eleven month after the surgery, the girl's appearance was less masculine, with significantly reduced body hairs but still no changes in the voice	No recurrence
Pereira et al. (31)	5.8	F	Weight gain, precocious puberty	3.2 cm x 4.5 cm	Open adrenalectomy	The patient is in complete remission after 64 month of follow-up	No recurrence
Kolev et al. (32)	9	F	Deepening of the voice and excessive hair	3 cm x 2.8 cm x 3.5 cm	Laparoscopic surgery	Normal hormone levels 2 week after operative resection	No recurrence
Agarwal and Agarwal (33)	2.5	F	Virilization	-	Open adrenalectomy, biopsy	Poor prognosis	No resection, infiltration into adjacent organs

increased awareness by pediatricians can play an important role in the early diagnosis and treatment of this disease.

Ethics

Informed Consent: Written consent was obtained from patient's family for this case.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.B., G.Ç., B.E.F., H.M., İ.A., R.M., D.K., B.N.D., Design: S.B., G.Ç., B.E.F., H.M., İ.A., R.M., D.K., B.N.D., Data Collection and/or Processing: S.B., G.Ç., B.E.F., H.M., İ.A., R.M., D.K., B.N.D., Analysis and/or Interpretation: S.B., G.Ç., B.E.F., H.M., İ.A., R.M., D.K., B.N.D., Writing: S.B., G.Ç., B.E.F., H.M., İ.A., R.M., D.K., B.N.D.

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