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Original Articles

Turkish Journal of Pediatric Disease

Original Article

The Association Between Maternal and Child Nutritional Status: Evidence From a Social Pediatrics Outpatient Clinic

Aylin BAYINDIR GÜMÜŞ[1], Seda Nur KÖKTÜRK[2], Hülya YARDIMCI[2], Aysun KARA UZUN[3], Nevra KOÇ[4]

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ABSTRACT

Objective: This study aimed to investigate the relationship between maternal and child nutritional status, considering the importance of children's nutrition at an early age.

Material and Methods: Mother-child pairs who attended a social pediatrics outpatient clinic participated in the study. A survey form was used to collect data, including questions regarding general information, breastfeeding, complementary feeding, and dietary records. The 24-hour dietary recall method was used as a dietary assessment method. Height and body weight were taken using measurement techniques by researchers. Data of pairs were collected from mothers, and they assisted in taking anthropometric measurements of the children. The recorded data were used to calculate the percentage of daily energy and nutrient requirements met by each participant. Pearson correlation analysis was performed to detect the coefficients of the relationship in SPSS statistic package program.

Results: The study included 104 mother-child pairs. The mean age of the mother and children was 30.7±5.7 years and 41.7±17.3 months, respectively. While 13.5% of the mothers were obese, 16.3% of the children were obese. A significant relationship was found between mothers' and children's daily main and snack numbers. The percentage of meeting their energy and protein requirements did not vary according to breastfeeding and complementary feeding parameters. Statistical analysis results showed significant relationships between percentages of meeting their macro and micronutrient requirements of mother-child pairs, except for energy and magnesium.

Conclusion: The study's results indicate that there is a relationship between the nutritional status of mothers and their children. There is a need for further research investigating the nutritional status of both mothers and children and emphasizing the interdependency of nutrition within the family.

Keywords: Mother-child pairs, Nutritional intakes, Parent diet

INTRODUCTION

The change in food preferences is a process that starts with pregnancy and continues throughout life. This development occurs with complex biological tendencies, and social and environmental factors (1). Various taste and flavor experiences in early stages of life play a role in promoting healthy eating later in life (2). Human milk is the first food consumed in infancy and accepted as the gold standard which has positive health effects for children (3). A systematic review found that optimal breastfeeding practices reduce morbidity and mortality from infectious diseases (gastrointestinal diseases, lower respiratory tract infections, allergic diseases) in the short term, and current evidence shows that they are effective in the long term against the emergence of non-communicable diseases, especially in high-income countries

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

Ethics Committee Approval : This study was conducted in accordance with the Helsinki Declaration Principles. This study was approved by the Ethics Committee of Ankara City Hospital and then Ankara University Rectorate (12.05.2020-No. 07/112).

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(4). Beyond these health effects, there is also evidence showing that breastfeeding can affect future food choices (5,6). Additionally, some factors such as the time when complementary feeding began, and the consumption of formula have also some effects on children's later food preferences (6).

At this point, parents, especially mothers who give primary care to children become active. Parents provide their children with food, feeding environments and experiences. Moreover, they prepare the social and physical environment by encouraging, setting, or preventing their children from consuming certain foods (7). Children can take their parents as role models in terms of their eating behavior, lifestyles, attitudes related to eating, and satisfaction with body image (2). As a result of these factors, it is thought that the nutritional habits of the parents affect the food choice, food intake, and other issues related to children's diet (8,9). In addition, children of obese parents are at higher risk of becoming obese (10). It is reported that cases in which children's diet are controlled by parents and imposing their own attitudes of dietary intake on the children are also effective on the child's eating attitude (11). Besides, it is thought that healthy nutritional intake of parents will encourage their children to do so (12).

This study hypothesizes that the nutritional status of mothers, who are responsible for the primary care of children has close relationships with children, and it also influences the nutritional status of the children. The nutritional status of mothers is remarkably crucial because the eating habits acquired in childhood continue throughout adulthood (13). This study aimed to determine the relationship between mother-child pairs' nutritional status.

MATERIALS and METHODS

Mother-child pairs who attended the Social Pediatrics Outpatient Clinic of the Ankara City Hospital were included in the study. The inclusion criteria for mothers were that being volunteer and not having communication problems to participate in the study. The exclusion criteria were not to be a volunteer for herself and/or her child. Consent forms were obtained from the volunteers participating in the research. For their children, the criteria were to have permission from their family to participate in this study. They needed to be between 9-72 months, not to have any diagnosed chronic or metabolic diseases, and to be cared for and fed by their mothers. The maximum number of samples reached that met the inclusion criteria within the data collection time (3 months) was included in the study. Adequacy of the sample size and power of the study was calculated using freely available open-source software, OpenEpi web tool (14), with a 95% confidence interval (CI) and 80% power, and it was determined that at least 53 mother-child pairs (106 in total) were adequate. This study was conducted with 104 pairs (208 children and their mothers in total).

The questionnaire form included general information about the children and mothers, questions about breastfeeding, nutritional habits of children, their mothers, and their families. Anthropometric measurements (body weight, height/length) of the children and their mothers were taken and evaluated according to WHO reference values by the researchers. For children up to 24 months, the height was measured by two people, ensuring that the child's heel and head touched the infantometer, with the knees tense. When the scale needle was fixed, body weight was measured with a digital baby scale. Both measurements were made lying down and with minimal clothing. For children above 24 months and mothers, the height was measured with a stadiometer, and body weight was taken with a digital scale, in Frankfurt plane and standing. When evaluating the measurements, WHO Anthro (version 3.2.2) percentile values were used for children. The percentiles of children's Body mass index (BMI) were classified as < 3 (severely underweight), 3-15 (underweight), 15-85 (normal), 85-97 (overweight), and >97 (obese). Body mass index (BMI) (body weight, kg)/(body height, m^2) values were calculated and assessed according to WHO – 2008 criteria: BMI of < 18.5 kg/m^2 (underweight), 18.5-24.9 kg/m^2 (normal weight), 25 – 29.9 kg/m^2 (overweight), and 30 – 39.9 kg/m^2 (obese) (14). Mothers' and children's 24-hour dietary recalls, describing and quantifying the intake of foods and beverages consumed in the 24 hours, the day before the interview, from the first intake in the morning until the last foods or drinks consumed at night, were recorded. All information was obtained from mothers in detail. The Nutrition Information System Program (BeBiS, Version 8.2) analyzed for energy and nutrient composition (16). Nutritional assessment was examined in reference to Dietary Guidelines for Türkiye (17). The percentages of meeting the daily requirement of each mother and child were calculated by following the requirements recommendation according to sex and age.

Participants were informed before starting the data collection and written consent was signed by volunteers both for them and their children. This study complied with the Helsinki Declaration and was approved by Ankara City Hospital and then by the Ethics Committee of Ankara University Rectorate (12.05.2020-No. 07/112).

Statistical Analysis

Data analysis was performed via IBM Statistical Package for the Social Sciences, version 26.0 (SPSS Inc., Armonk, NY, IBM Corp., USA) for the Windows package program. Mean and standard deviation (SD) were calculated for the quantitative data. The distribution of data was given with tables of numbers (n) and percentages (%). The Pearson Chi-Square test was used to determine whether there was a significant difference between the frequencies. The regularity of the distribution for each parameter was evaluated using the Kolmogorov-Smirnov test. Data obtained from this study showed normal distribution (17). Independent sample t test and One Way ANOVA test were used to compare the means between two independent groups and more than two independent groups. Pearson correlation analysis was used to determine the relationship between two variables. The correlation coefficient was evaluated as follows: 0.00-0.10 (negligible), 0.10-0.39 (weak), 0.40-0.69 (moderate), 0.70-0.89 (strong), and 0.90-1.00 (perfect)

RESULTS

Total of 104 mother-child pairs were included in the study, and 58.7% of the children were girls. The mean age of mothers was

Table I: Characteristics of Mother-Child Pairs

Characteristics	Mothers (n=104)	Children (n=104)
Age, mean (SD)*	30.7±5.7 years	41.7±17.3 months
Girl†	104 (100)	61 (58.7)
BMI, mean (SD)‡	25.3±4.6 kg/m^2	59.2±32.7
Overweight†	37 (35.6)	17 (16.3)
Obese†	14 (13.5)	17 (16.3)

: mean±standart deviation,†: n(%), ‡: Reported as percentile of BMI for age for children, **BMI: body mass index*

Table II: Dietary Habits of Mother-Child Pairs

Dietary habits	Mothers	Children	p
Main meal*			
1 or 2	45 (43.3)	9 (8.7)	<0.001‖
3	59 (56.7)	95 (91.3)	
Snack*			
No or 1	53 (51.0)	13 (12.6)	<0.001‖
2	38 (36.5)	46 (44.2)	
3 or above	13 (12.5)	45 (43.2)	
The duration of each main meal (minute)†	21.0±12.5	21.9±15.2	0.651¶
Most common preferred food in snacks (Fruit)*	(36, 34.6)	(65, 62.5)	-
Most common preferred drink in snacks*	(32, 30.8)‡	(36, 34.6)§	-

**: n(%), †: mean ±standart deviation, ‡: tea, §: milk, ‖: Pearson Chi-square test, ¶: Independent sample t test*

30.7±5.7 years and the mean age of children was 41.7±17.3 months. While 49.1% of mothers and 32.6% of children were overweight/obese, respectively (Table I).

In examining some dietary habits of participants, most of the mothers (56.7%) and children (91.3%) had consumed 3 main meals. There was a significant difference between frequencies of the number of both main meals and snacks for children and their mothers. The mean duration of each main meal was not statistically different between mothers and children (p>0.651). While the most common preferred food in snacks was fruit for both mothers and children, the drink was tea and milk for mothers and children, respectively (Table II).

The percentages of meeting energy and protein requirement of mothers and their children did not differ according to the duration of exclusive breastfeeding (p=0.678, p=0.479, p=0.917, p=0.990), first breastfeeding time (p=0.456, p=0.313, p=0.674, p=0.052), main food source in 6 months of life (p=0.982, p=0.259, p=0.991, p=0.564), and the day complementary nutrition started (p=0.642, p=0.201, p=0.923, p=0.326) (Table III).

There were positive correlations between mothers and children in terms of the mean percentages of meeting protein (r=0.313, p=0.001, weak), dietary fiber (0.359, p<0.001, weak), calcium (r=0.343, p<0.001, weak), phosphorus (0.364, p<0.001, weak), iron (r=0.298, p=0.002, weak), zinc (r=0.564, p<0.001, moderate), vitamin A (r=0.654, p<0.001, moderate), vitamin E (r=0.367, p<0.001, weak), vitamin K (r=0.539, p<0.001, moderate), vitamin C (r=0.509, p<0.001, moderate), thiamine (r=0.397, p<0.001, weak), riboflavin (r=0.487, p<0.001, moderate), niacin (r=0.426, p<0.001, moderate), pyridoxine (r=0.240, p=0.014, weak), folate (r=0.504, p<0.001, moderate), vitamin B12 (r=0.965, p<0.001, perfect) (Table IV) requirements.

Table III: The Percentages of Meeting Energy and Protein Requirements According to The Features of Children

	Energy (kcal)				Protein (g)			
	Mothers*	p†	Children*	p†	Mothers*	p†	Children*	p†
The duration of exclusive breastfeeding								
0-3 months	67.3±23.0	0.678	77.5±24.2	0.479	106.8±30.2	0.917	250.4±87.1	0.990
4-6 months	70.8±23.8		86.5±31.7		108.9±39.0		253.5±111.8	
>6 months	62.6±10.1		86.6±40.5		115.0±14.4		257.0±105.6	
First breastfeeding								
0-30 min	70.3±23.1	0.456	86.6±33.1	0.313	110.5±36.2	0.674	266.6±114.2	0.052
31-60 min	63.9±20.2		82.4±22.3		102.5±37.0		219.1±59.0	
≥61 min	75.4±29.5		70.5±10.7		104.0±40.6		193.0±50.1	
The main food in the 6 months period of life‡								
Exclusive breastfeeding	69.4±23.7	0.982	88.5±29.0	0.259	109.7±39.3	0.991	263.3±113.0	0.564
Breastfeeding and formula	71.4±23.6		84.2±31.4		107.4±28.9		250.1±82.5	
Breastfeeding and complementary foods	68.7±22.6		72.1±33.6		107.2±39.3		223.1±114.0	
The day of starting complementary nutrition								
<180th	70.0±23.6	0.642	74.6±30.7	0.201	107.0±36.0	0.923	229.1±103.4	0.326
180th	67.0±21.8		89.4±33.8		107.6±41.0		271.5±117.9	
>180th	71.9±24.3		85.3±27.1		110.3±33.4		249.0±96.1	

**: mean±standart deviation, †: One Way ANOVA test ,‡: Excluded one child who fed only formula and his mother*

Table IV: Correlation of The Percentages of Meeting Energy and Nutrient Requirements of Mother-Child Pairs, Mean (SD)

Nutrients	Mothers*	Children*	Coefficient	p†
Energy	69.8±23.2	84.6±30.5	0.170	0.085
Protein[a]	108.7±36.5	253.0±105.9	0.313	0.001
Dietary fiber	68.3±37.1	58.4±26.2	0.359	<0.001
Ca	58.2±26.1	70.4±36.0	0.343	<0.001
P	114.9±39.0	155.3±60.9	0.364	<0.001
Fe	48.3±19.7	82.5±35.5	0.298	0.002
Zn	104.3±61.9	236.7±170.2	0.564	<0.001
Mg	69.1±28.3	165.9±70.7	0.159	0.108
Vitamin A	128.4±161.0	207.8±196.4	0.654	<0.001
Vitamin E	73.6±38.9	129.6±94.3	0.367	<0.001
Vitamin K	112.1±203.7	185.5±353.1	0.539	<0.001
Vitamin C	86.3±69.1	130.9±109.6	0.509	<0.001
Vitamin B_1	62.3±26.3	112.0±49.1	0.397	<0.001
Vitamin B_2	83.7±36.5	225.4±137.8	0.487	<0.001
Vitamin B_3	70.4±36.6	109.2±69.9	0.426	<0.001
Vitamin B_6	66.0±26.1	167.3±109.1	0.240	0.014
Folate	58.2±29.4	110.0±62.8	0.504	<0.001
Vitamin B_{12}	163.9±453.2	398.9±925.1	0.965	<0.001

***:** *mean ± standart deviation,* **†:** *Pearson correlation test,* ***Ca:** Calcium, **P:** Phosphorus, **Fe:** Iron, **Zn:** Zinc, **Mg:** Magnesium*

DISCUSSION

This study was carried out to examine the relationship between the nutritional status of children and their mothers. While the frequencies of the main meals and snacks of children differed from their mothers, the mean times of the main meals were similar. Mother-child pairs most frequently consumed fruit in snacks, however, as beverages children and mothers drank milk and tea, respectively.

In current study, positive correlations were found between the percentages of meeting daily calcium, iron, thiamine, and folate requirements of mothers and children. However, studies in the literature are generally based on the comparison of food preferences and percentages of energy and macronutrient intakes of parent(s)-child(ren) pairs (20,21). The number of studies comparing micronutrients is limited. In this respect, the results of this study are preliminary data for future studies.

In this study, the percentage of mothers meeting their daily energy requirements was 69.8%, and it was not found to be correlated to their children's. A study, conducted by Aksoy and Garipağaoğlu (20) demonstrated that daily energy requirements were met at 93.0% and 83.4% for children and their mothers, respectively. While Aksoy and Garipağaoğlu's (20) study was conducted in a private hospital, this study was conducted in a public hospital, and it was thought that the difference between the percentages was due to the economic status.

Robson et al. (21) provided some evidence that the daily energy intake of the parents explained 21% of the child's energy intake. In the study of Robinson et al. (22) it was reported that there were weak correlations between both the energy intake of children aged 8-12 and their mothers and the percentage of energy from proteins of the same groups. However, no relationship was found for other macronutrients. In addition, it was revealed that as the amount of dietary fat in the parent's diet increased, the amount of fat in the child's diet also increased (23). In a study, it was determined that there was no difference between the daily energy intake of mothers and their children and the percentage of energy coming from protein, but the percentage of energy coming from fat was different (24). In a study conducted in the United States, the energy intake of parents and children through diet, the percentage of energy coming from fat, saturated fat, cholesterol, sodium, calcium, and fiber were examined and it was reported that this relationship was weak (25).

In a meta-analysis study that included 15 studies, it was determined that the correlation value between the nutrient intakes of mothers and children varies depending on the dietary evaluation and the country where the research was conducted. It was found that the correlation coefficient was lower in studies based on children's self-reporting (9).

Since preschool children cannot prepare their own food, they are dependent on their parents in this regard. They also tend to consume the same foods as their parents. Therefore, the correlation between the percentages of meeting nutrient requirements of parents and children is an expected finding.

Similarities can be observed between the food preferences of parents (especially mothers) and children as well. In the study of Vivarini et al. (26) a positive relationship was detected between the amount of fruit consumption by mother-child pairs. Similarly, another study conducted in Australia showed that the amount of fruit consumption of mother-child pairs was correlated. (27). Walsh et al. reported that as fruit consumption by fathers increased, it also increased by their children similarly (28). In a meta-analysis, the consumption of sugar-sweetened beverages and fruit and vegetables by children was like the consumption by their parents (29). In addition, Vaughn et al. (30) reported that the diet quality of the children who had healthy eating patterns was higher. In a study conducted with girls, it was reported that having a healthy diet for children was highly correlated with the mothers' diet (31). These studies showed that the diet of parents, especially mothers, considerably influences the diet of the child. In this study, the relationship on the basis of foods was not examined. However, since nutrient intakes reflect food intake, it is thought that the nutritional consumption of the mother and child will have similar results to those of these studies. In this study, some nutritional intakes of mothers and children are similar. Another study unveiled that the diet of the children was more like the diet of the parents who responded to the food intake record (32). This made us think that the results of food consumption records of children might vary according to the responder. Possible mistakes on this issue are another limitation of this study. In future studies, it is thought that food consumption records should be obtained from both parents and primary caregivers separately and independently.

In this study, the percentage of dyads meeting their daily energy and protein requirements did not vary based on breastfeeding or complementary feeding parameters. Shim et al. (33), have shown that the duration of breastfeeding and the timing of introducing complementary foods influence children's food choices during the preschool years.

It is reported that as the duration of breastfeeding increases, children eat healthier in the future (34). In addition, the consumption of vegetables when they reached the age of 2-4 years was higher in children who were breastfed for the first 3-6 months in life compared to those who were breastfed for a shorter period (35). Another study found that children who were breastfed for at least 3 months consumed more fruit when they were 6 years old than those who had never been breastfed (36). However, the data of this study was cross-sectional, and the nutritional status of the children in the following years was not kept track. This situation could be thought of as a study limitation.

CONCLUSION

Not having the ability to meet their self-care and being dependent on at least one caregiver (generally their mothers) cause children to be more affected by environmental factors. Therefore, it is inevitable that the nutritional status of children is affected by parents, and they play a crucial role in having a healthy diet for children. It is supported by the results of this study that especially the nutritional status of the mothers affects their children. Thus, it is important to improve the nutritional status of parents. In addition, nutritional habits acquired in childhood become permanent, continue in later years, and affect children's health status. However, it would be useful to carry out studies including mothers, fathers, and other family members to clarify this situation.

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Original Article

Impact of the COVID-19 Era on Phenylalanine Levels and Classical Phenylketonuria Patients Follow-Up: A Retrospective Analysis

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ABSTRACT

Objective: Phenylketonuria is a metabolic disorder resulting from mutations in the *PAH* gene, causing elevated blood phenylalanine (Phe) levels which can lead to severe neurological damage if untreated. The primary treatment is a lifelong low-protein diet with amino acid substitutes and micronutrient supplements. During the COVID-19 pandemic, classical phenylketonuria (PKU) patients faced significant challenges, including restricted access to routine care like clinical visits and metabolic control monitoring. The aim of the this study was to examine the disruptions in outpatient visits, the variances in pre- and post-pandemic Phe levels, and clinical severity among patients who contracted COVID-19.

Material and Methods: Starting from the pandemic date of March 11, 2020, demographic data, laboratory characteristics, and details about COVID-19 infection were retrospectively reviewed for classical PKU patients with accessible electronic records from March 2018 to March 2022.

Results: When the median blood Phe levels before and after the pandemic were compared, a significant difference was found. We observed that adult patients diagnosed with classical PKU often defaulted on their follow-up appointments.

Conclusion: The COVID-19 pandemic significantly disrupted the follow-up and management of classical PKU patients. However, no severe COVID-19 cases were reported among this population, suggesting they did not face an increased risk from the infection. This study emphasizes the critical need to develop robust strategies for patient engagement and follow-up, especially for adult classical PKU patients who are at risk of discontinuing routine care.

Keywords: Classical phenylketonuria, COVID-19, Phenylalanine levels, SARS-CoV-2

INTRODUCTION

Phenylketonuria (PKU; OMIM 261600) is a metabolic disorder caused by mutations in the PAH gene, which encodes the liver enzyme phenylalanine hydroxylase (PAH). This enzyme typically converts the amino acid phenylalanine (Phe) into tyrosine. A deficiency in PAH activity leads to elevated blood Phe levels, which can reach toxic concentrations and primarily affect the central nervous system (CNS). If untreated, symptoms such as neurological impairment, psychomotor delay, seizures, autism, and behavioral disorders can develop soon after birth (1,2). The primary treatment is a lifelong dietary intervention to ensure normal growth and neurodevelopment. This diet includes low-protein foods, amino acid substitutes, and micronutrient supplements. Türkiye has the highest prevalence of PKU, partly attributed to the high incidence of consanguineous marriages (3).

In recent times, the world faced the COVID-19 pandemic, one of the most significant global health disasters of the century. The World

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

Ethics Committee Approval : This study was conducted in accordance with the Helsinki Declaration Principles. This study received approval from the Hacettepe University Ethics Committee for Non-Interventional Clinical Studies (GO22/176, 2022/08–23).

Contribution of the Authors ***KAHRAMAN AB:*** Conception, Design, Data Collection and Processing, Analysis and Interpretation, Literature Review, Writing, ***YILDIZ Y:*** Design, Supervision, Critical Review, ***GEÇİCİ NN:*** Data Collection and Processing, ***ÇIKI K:*** Data Collection and Processing, Critical Review, ***ERDAL İ:*** Data Collection, ***AKAR HT:*** Data Collection, ***DURSUN A:*** Supervision, Critical Review, ***TOKATLI A:*** Supervision, Critical Review, ***SİVRİ HS:*** Supervision, Critical Review

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Health Organization (WHO) proclaimed COVID-19 a pandemic on March 11, 2020. Following the first reported case, many countries declared implementing quarantine measures. Ensuring continuous care for patients with intricate health requirements, particularly those with rare diseases, has emerged as a significant challenge for healthcare providers during the COVID-19 pandemic.

During the COVID-19 pandemic, PKU patients faced unprecedented challenges, including severely restricted access to routine care such as in-person clinical visits, metabolic control monitoring, and self-sampling blood tests. Additionally, there was significant uncertainty surrounding their ability to obtain essential medical supplies and specialized low-protein food. Due to their need for special dietary products, the pandemic was a challenging period for PKU patients. In the study conducted by Akar et al. (4), it was shown that 61.2% of patients with classical PKU were more anxious.

While we have made substantial strides during the COVID-19 pandemic, there is no assurance against future pandemics. This unprecedented period has imparted critical lessons for the innovation of our healthcare system, one of the most pivotal being the integration of telemedicine. Our understanding of the ongoing pandemic remains incomplete, underscoring the need for continuous knowledge expansion to confront prospective challenges. Within this framework, we sought to analyze the implications of the pandemic on classical PKU, a prevalent inherited metabolic disorder in Türkiye. Our study examined the disruptions in outpatient visits, the variances in pre- and post-pandemic Phe levels, and clinical severity among patients who contracted COVID-19.

MATERIALS and METHODS

This study received approval from the Hacettepe University Ethics Committee for Non-Interventional Clinical Studies (GO22/176, 2022/08–23). Classical PKU was defined as untreated Phe levels above 20 mg/dL (1200 µmol/L) (5). In the two-year follow-up before and after March 11, 2020, when the pandemic was declared, the average of blood Phe values and the number of admissions were recorded and compared. Additionally, the study included patients who tested positive for SARS-CoV-2 PCR or antibodies. The patients were reached through phone calls and invited to participate in a survey that obtained demographic data and details about COVID-19 infection. Informed consent was obtained from all participants or their parents/guardians.

Inclusion and exclusion criteria

The start date of the pandemic was considered to be March 11, 2020. The patients with diagnosed disorders of Phe metabolism, for whom electronic health record data was accessible between March 2018 and March 2022, were reviewed retrospectively. Patients diagnosed with classical PKU through molecular analysis, who require dietary intervention and are under follow-up at our department (Hacettepe University, Pediatric Metabolism Unit) were included in this study. The patients with diagnosed mild hyperphenylalaninemia, pregnancy, and tetrahydrobiopterin (BH4)-responsive PKU were considered as exclusion criteria due to potential biases related to their different follow-up frequencies.

Demographic data, laboratory characteristics, and information related to COVID-19 infection were extracted retrospectively from the patients' electronic medical records. Additionally, patients who tested positive for SARS-CoV-2 via PCR or antibody tests were identified and included in the study. These patients were contacted by phone and invited to participate in a survey to obtain further details about their COVID-19 infection and overall health during the pandemic. The number of outpatient visits and blood Phe levels before and after the pandemic were recorded and compared to assess the impact of the pandemic on metabolic control and patient follow-up.

Statistical Analyses

The data were analyzed by IBM SPSS Statistics Version 25.0 (IBM Corp., Armonk, NY, USA). The normality of the variables was investigated by visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk tests). Descriptive statistics were presented as mean, standard deviation, median, range (minimum-maximum), interquartile range (IQR), and frequencies. Since the blood Phe level and admission number were not normally disturbed; nonparametric tests were conducted to compare these parameters. The Wilcoxon test was used to compare the change in admission number and blood Phe level between pre-pandemic and post-pandemic period. A p value of less than 0.050 was considered to show a statistically significant result.

RESULTS

Since 2018, our department has been following up 1960 patients diagnosed with PKU, hyperphenylalaninemia, or BH4-responsive PKU. Of these, 809 patients with classic PKU were included in the study after excluding 1151 patients with HPA or BH4-responsive PKU. Among the total cohort (n=1960), we had a total of 118 patients who contracted COVID-19. Of the 118 patients, 25 classic PKU patients were 'lost to follow-up,' who did not have any blood Phe level measurements before or after the pandemic, and could not be contacted. These patients were excluded. Additionally, 16 patients diagnosed with BH4-responsive PKU and HPA, as well as five patients with pregnancy-classic PKU, were excluded. Patients without mild hyperphenylalaninemia or BH4-responsive PKU and those not being followed up for pregnancy with a more frequent protocol than usual were included in the study. Seventy-two patients with classical PKU who had contracted COVID-19 were included in the study. Among the 809 patients with classic PKU, 72 who had contracted COVID-19 were included in the study. The flowchart of participants is shown in Figure 1.

The characteristics of the patients with classical PKU are given in Table I. There were 420 patients aged 18 and over, and 389 patients under the age of 18. There was a significant difference in the number of Phe measurements before and after the pandemic. The median number of Phe measurements before the pandemic was 4 (1-41), while after the pandemic it decreased to 2 (1-59) ($p<0.001$). Furthermore, the median Phe levels before the pandemic were 10.4

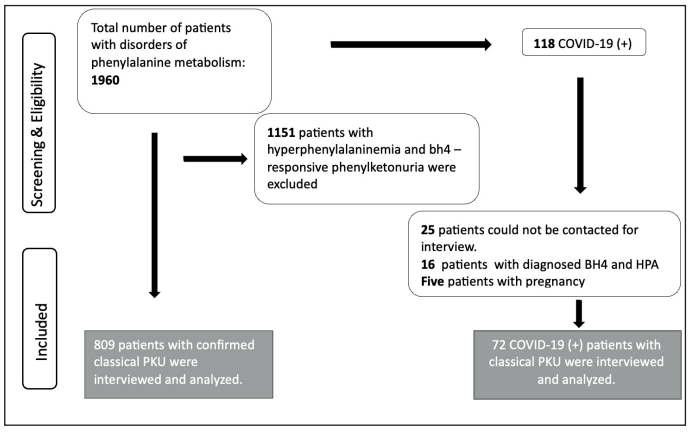

Figure 1: Flowchart of patients. **BH4:** Tetrahydrobiopterin responsive phenylketonuria, **COVID-19 (+):** Coronavirus disease 2019, **HPA:** Hyperphenylalaninemia, **PKU:** Phenylketonuria.

Table I: Characteristics of the classic phenylketonuria patients

		p
Age, years*	18 (1-49)	-
Sex, Female/Male (n)	361/448	-
Number of Phenylalanine measurements*		
Pre-Pandemic (n=809)	4 (1-41)	<0.001†
Post-Pandemic (n=707)	2 (1-59)	
Phenylalanine level*		
Pre-Pandemic (n=809)	10.4 (0.86-38.4)	<0.001†
Post-Pandemic (n=707)	9.1 (0.51-29.4)	

***:** *median (minumum-maximum),* **†:** *Wilcoxon test,*

mg/dL (0.86-38.4), and this decreased to 9.1 mg/dL (range: 0.51-29.4) after the pandemic (p<0.001). There was a 12% decrease in the number of follow-up Phe measurements of patients with classical PKU. Among 102 patients lost to follow-up, the median age was 18 years (3–36), with a female-to-male ratio of 48:54. The median number of phenylalanine measurements was 2 (1–42), and the median phenylalanine level was 15.8 mg/dL (1.4–35.9).

Among the 72 classic PKU patients who contracted COVID-19, the median age was 21 years. When the median blood Phe levels before and after the pandemic were compared, a significant difference was found (9.3 [1-27] vs. 9.0 [2.0-24.8], respectively, p=0.025). However, there was no significant difference in the number of Phe measurements before and after the pandemic (3 [1- 27] vs. 3 [1-16], respectively, p=0.750) (Table II).

The clinical features of patients with classical PKU who contracted COVID-19 are provided in Table II. None of the patients were admitted to the intensive care unit or required invasive mechanical ventilation. No patient was deceased. Regarding the clinical spectrum of COVID-19 among these patients, 12 (16.7%) were asymptomatic, 56 (77.8%) had mild illness, and four (5.6%) experienced moderate illness. Hospitalization was required for only three patients (4.2%), and two patients (2.8%) needed oxygen therapy. Feeding difficulties were reported in 20 patients (27.8%).

Table II: Characteristics of classical phenylketonuria patients with COVID-19 positive (n=72)

		p
Age, years*	21 (2-43)	-
Age group†		
Child	30 (41.7)	-
Adult	42 (58.3)	
Sex†		
Male	35 (48.6)	-
Female	37 (51.4)	
Phenylalanine level pre-pandemic (mg/dl)*	9.3 (1.7-26.7)	0.025‡
Phenylalanine level post-pandemic (mg/dl)*	9.0 (2-24.8)	
Number of Phenylalanine measurement pre-pandemic*	3 (1-27)	0.075‡
Number of Phenylalanine measurements post-pandemic*	3 (1-16)	
Clinical Spectrum of COVID-19*		
Asymptomatic:	12 (16.7)	-
Mild Illness:	56 (77.8)	
Moderate Illness:	4 (5.6)	
Hospitalization*		
Yes	3 (4.2)	-
No	69 (95.8)	
Oxygen requirement*		
Yes	2 (2.8)	-
No	70 (97.2)	
Feeding difficulties*		
Yes	20 (27.8)	-
No	52 (72.2)	

:** *median (IQR),* **†:** *n(%),* **‡:** *Wilcoxon test,* ***Phe: *Phenylalanine,*

DISCUSSION

In the management of PKU treatment, the aim is to keep Phe levels under control throughout life, along with adherence to the diet, to achieve positive neurocognitive outcomes. The COVID-19 pandemic posed significant challenges for the follow-up and management of patients with PKU. Studies are showing increased stress levels and treatment noncompliance among PKU patients and their parents during the pandemic (4,6). The challenges faced by patients in accessing special dietary products during the pandemic were notable, highlighting the need for robust supply chain mechanisms to ensure continuous access to necessary dietary products. Additionally, the frequency of outpatient visits, dietary assessments, and frequent biochemical monitoring requirements cause patients to be lost to follow-up even outside of the pandemic. As patients age, the likelihood of being lost to follow-up care significantly increases (7). This study highlights several critical insights from a single-center experience regarding the metabolic control and follow-up status of PKU patients.

One notable finding from our study is the difficulty in maintaining follow-up for adult PKU patients. The median age of our patients who discontinued follow-up is 18, and they were who generally already had poor metabolic control. Many adult patients discontinued their regular monitoring during the pandemic. As a reference center, we have patients from many cities across our country. We anticipated that the geographical limitations in transportation would cause

some of our patients to lost-follow-up during the pandemic period. This gap in follow-up is concerning given the potential for long-term complications if metabolic control is not maintained.

Similar to the study by Walkoviak et al. (8), patients who were non-compliant with their follow-ups in the past were more likely to drop out of follow-up, while those who continued their follow-ups did not experience an increase in Phe levels. Herle et al. (9), reported that school-aged patients sent fewer samples during the COVID-19 period, and patients over the age of 16 sent significantly fewer dried blood spots samples in 2020. As patients get older, they may exhibit a tendency to miss follow-ups due to the need to manage their diet independently of their parents, and because they are more susceptible to the influences of their social environment and work life. Previous studies have also investigated the reasons why patients lost follow-up, highlighting factors such as lack of insurance and financial resources, difficulties in accessing metabolism centers due to economic problems, and reluctance to return to a restricted diet (10). Additionally, adult patients may not want to wait in the same clinic as children and may no longer perceive the disease as a serious issue.

Reaching adulthood from the newborn screening period without mental disability is possible with a significant amount of labor, time, and money from the healthcare system and with the efforts of dedicated families. To sustain this effort for the development of an independent, productive, and stable society, we must continue to remind our adult patients who have lost follow-up care, their value and the importance of continuous treatment. For adult patients, transition services, or solutions like telemedicine during crises such as the pandemic, as well as overcoming physical and economic challenges due to the limited number of metabolic disease management centers in our country, can be crucial. Implementing telemedicine for routine follow-ups can improve adherence to treatment plans and ensure consistent monitoring. Studies from various centers have shown that telemedicine effectively maintains patient engagement and metabolic control, with high patient satisfaction. It was highlighted that telemedicine played a crucial role in re-engaging patients who had lost follow-up, bringing them back into regular monitoring (11). These findings suggest that telemedicine could be a valuable tool for long-term management of PKU, particularly during the pandemic. The feedback from patients in these studies was overwhelmingly positive, suggesting that telemedicine could be a valuable tool in the long-term management of PKU (12-16). These measures can help prevent them from lost follow-up and ensure the continuity of their metabolic control.

Interestingly, we found a significant improvement in median blood Phe levels during pandemic. This could be attributed to the reduced social distractions and increased focus on dietary compliance during lockdown periods. Previous research supports this observation, indicating that adolescents and adults had better metabolic control during lockdown due to fewer social interactions and temptations that might lead to dietary lapses. Due to the requirement to leave their homes only for emergencies, patients were compelled to consume homemade meals instead of dining at restaurants or eating out. In the study conducted by Rovelli et al. (17), which included 192 patients, the median Phe level decreased by 22.5% during the pandemic ($p<0.001$). Zubarioğlu et al. (18) highlighted that during the pandemic, 92 patients had better Phe levels, applied fewer washout diets, and attributed this to the benefits of telemedicine applications. In the study conducted by Herle et al. (9), which included 77 PKU patients, no change in Phe levels was observed during the pandemic period. However, a significant decrease in number of Phe measurements was observed, particularly in patients over the age of 16. In the study conducted by Becsei et al. (19), which included 83 patients with classical PKU, an increase in Phe levels was observed in adolescents during the non-pandemic period. Similar to other studies, it has been reported that the number of measured Phe levels decreased, and some patients lost follow-up (9). We believe that the significant decrease in the number of measured Phe levels can be attributed to the postponement of appointments due to the chronic nature of the disease. At this point, collaborating with local healthcare services and ensuring that patients continue their blood tests via mail could be a solution.

During the COVID-19 pandemic, parents of children with classical PKU were concerned about increased risks and sought guidance. We informed them that no specific data linked PKU to higher COVID-19 risk, emphasizing that severe illness was more common in those with advanced age, male gender, or chronic conditions (20). Our findings indicated that PKU patients did not face higher severe COVID-19 risks, with none of our monitored patients experiencing severe illness. Despite disruptions in metabolic monitoring and dietary management, PKU patients' clinical outcomes were not significantly affected by COVID-19.

The limitations of our study are its retrospective design and the lack of information on Phe levels if patients provided these measurements at other centers. During the active COVID-19 infection period, we were unable to consistently monitor the Phe levels of our patients. The strength of our study lies in its inclusion of the largest sample size in the literature and having the highest number of PKU patients who contracted COVID-19.

In conclusion, the COVID-19 pandemic has underscored the importance of adaptable healthcare delivery models. Ensuring the continuity of care through innovative approaches like remote monitoring and telehealth consultations can mitigate the impact of future disruptions and improve overall patient outcomes. The insights gained from this single-center experience could inform broader healthcare strategies for managing chronic conditions in a during pandemic world. Healthcare services should intensify their efforts in enhancing adherence and monitoring strategies for patients with classical PKU. The results of our study could provide a valuable foundation for discussions on future potential scenarios. Future strategies should focus on enhancing telemedicine services, ensuring the availability of dietary products, and providing targeted support to different patient groups to improve overall care and outcomes for PKU patients. The lessons learned from this study can inform the development of measures to be implemented in the event of another possible lockdown. The healthcare system can organize more quickly when faced with a similar crisis.

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Original Article

Evaluation of the Effect of Diet Adherence on Nutritional Status and Metabolic Control in Children with Phenylketonuria Consuming a Phenylalanine-Restricted Diet: A Single-Center Study

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ABSTRACT

Objective: The aim of this study was to determine the dietary habits of patients with phenylketonuria (PKU) in different age groups, to assess energy, protein and phenylalanine intakes, and to evaluate dietary compliance and its effect on metabolic control.

Material and Methods: The study, conducted between 1 March 2022 and 30 September 2022, the study involved 20 children aged 2-18 diagnosed with PKU at the Department of Pediatric Metabolism Outpatient Clinic of Ankara Bilkent City Hospital. Participants were evaluated for diet compliance and had their blood phenylalanine and tyrosine levels were measured.

Results: Among the 20 patients, 42.9% (n=9) were female and 57.1% (n=11) were male, with a mean age of 4.7±3.22 years. Age distribution was 70% (n=14) aged 2-6, 20% (n=4) aged 6-10, and 10% (n=2) aged 10-13. Patients attended four follow-ups over six months. A moderate negative correlation was found between daily dietary phenylalanine and blood phenylalanine levels in the first and last controls, and a high negative correlation in the 2nd and 3rd controls ($p=0.006$, $p<0.001$, $p<0.001$, $p=0.013$). A positive moderate correlation was found between the frequency of daily amino acid mixture consumption and diet compliance ($p=0.025$). Increased meal frequency improved diet compliance. No significant relationship was found between blood phenylalanine levels and amino acid mixture consumption, diet compliance, or daily amino acid mixture consumption frequency.

Conclusion: In PKU, nutritional habits, daily phenylalanine intake and amino acid mixture consumption frequency impact dietary compliance and metabolic control. Lifelong medical nutrition therapy requires multidisciplinary team support, frequent follow-ups and adherence to the recommended diet.

Keywords: Metabolic control, Phenylalanine, Phenylketonuria

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

Ethics Committee Approval : This study was conducted in accordance with the Helsinki Declaration Principles. This study was approved by the Clinical Research Ethics Committee No. 2 of Ankara Bilkent City Hospital with the decision number E2-22-1349 dated 02.02.2022.

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INTRODUCTION

Phenylketonuria (PKU) is an inherited metabolic disease that develops as a result of deficiency or insufficiency of the phenylalanine hydroxylase (PAH) enzyme with an autosomal recessive inheritance (1). Due to PAH enzyme deficiency or insufficiency, phenylalanine cannot be converted to tyrosine and phenylalanine and can not be metabolized (2). As a result, toxic metabolites such as phenylalanine, phenylpyruvic acid, phenylacetic acid, phenylactic acid accumulate in the blood, brain and tissues, resulting in serious neurological complications and mental disability (3). In Türkiye, which is one of the countries where the disease is most common, it is aimed to prevent mental disability with early diagnosis and appropriate diet therapy with newborn screening (4).

In the treatment of phenylketonuria, restricting the amount of phenylalanine in the diet is the main effective method of controlling blood phenylalanine levels (5,6). With phenylalanine-restricted nutrition therapy, it is aimed to reduce the consumption of natural protein sources, to meet all other nutritional needs, especially the daily protein needs of patients, with special nutrition products and phenylalanine-free amino acid mixtures instead of natural protein sources (3).

Compliance with the diet of children with PKU who are on a phenylalanine-restricted diet constitutes the success of nutritional therapy. The fact that families play an active role in the implementation of the diet affects compliance with the diet (2,7). In patients about compliance with diet therapy, factors such as the education level of the family, insufficient knowledge about the disease and diet therapy, family culture, difficulties in consuming amino acid mixtures, dislike of the taste of special products or cooking problems, lack of access to special products due to insufficient social support are encountered (8).

It is known that metabolic control is positively affected by the increase in adherence to diet therapy; therefore, blood phenylalanine and blood tyrosine levels of patients should be closely monitored (3).

The aim of the study was to determine the nutritional habits, energy, protein and phenylalanine consumed by phenylketonuria patients in various age groups and to evaluate their compliance levels and its effect on metabolic control.

MATERIALS and METHODS

The study was conducted between 1 March 2022 and 30 September 2022 on 20 children between the ages of 2-18 who were followed up with the diagnosis of PKU in the department of Pediatric Metabolism Outpatient Clinic of Ankara Bilkent City Hospital Children's Hospital and consumed a phenylalanine-restricted diet in the Pediatric Metabolism Diet Outpatient Clinic who agreed to participate in the study.

This study was approved by the Clinical Research Ethics Committee No. 2 of Ankara Bilkent City Hospital with the decision number E2-22-1349 dated 02.02.2022. Before the application, the purpose of the research and the necessary information were explained to the participants by the researchers and the consent of the participants was obtained.

Patients in the 0-2 age group were not included in the study, while a total of 20 patients over the age of 2, who were being followed up with dietary treatment during the study period, were included. The number of patients who gave their consent and agreed to participate in the study was 20; since they were between the ages of 2-13, they were divided into 3 age groups as 2-6 years, 6-10 years and 10-13 years. The age groups in our study were determined as 2-6 years old preschool period, 6-10 years old primary school period and 10-13 years old adolescence period depending on the differences in the nutritional habits and needs of the patients. These patients were already being followed with dietary treatment, and their initial assessments were taken at the start of the study, followed by the 2nd, 3rd and 4th controls. The time interval between the study periods was 1-1.5 months.

A face-to-face questionnaire was applied to the patients, personal and disease-related data were recorded in this form. In the first part of the survey, patients' blood phenylalanine and tyrosine levels were examined, and their food consumption records were used to calculate the total daily protein intake from their diet, the amount of protein from amino acid mixtures, phenylalanine intake, and daily energy intake. Additionally, anthropometric measurements were taken and evaluated. In the second part of the survey; socio-demographic characteristics such as parental age, profession, educational status, social security, and questions such as whether there are other patients with PKU in the family, and the presence of a kinship relationship are included.

In the third part of the survey; the consumption of the amino acid mixture used, the level of knowledge about its consumption, and the difficulties experienced in its consumption were questioned. In the fourth part of the questionnaire, the consumption of special products, and in the fifth part, the frequency of daily meals and the level of compliance with the diet regarding general eating habits were questioned.

Statistical Analysis

As descriptive statistics, mean and standard deviation were used for continuous data, frequency and percentage were used for categorical data. The conformity of continuous data to the normal distribution was checked by the Kolmogorov-Smirnov test. The relationship between two continuous variables was evaluated by Pearson and Spearman correlation analysis, the relationship between ordinal categorical variables was evaluated by Spearman correlation analysis, the relationship between categorical variables was evaluated by Cramer's V correlation coefficient, and the relationship between continuous and bi-category variables was evaluated by Point biserial correlation coefficient. The cut-off points used for the interpretation of the obtained correlation coefficients are 0.00-0.19 very weak, 0.20-0.39 weak, 0.40-0.69 moderate, 0.70-0.89 high and 0.90-1.00 very high. The data were analyzed with the IBM SPSS 21 (IBM SPSS Inc, Chicago, IL) package program. Statistical significance level was taken as $p<0.050$.

RESULTS

Of the 20 patients who participated in the study, 42.9% (n=9) were female and 57.1% (n=11) were male. The majority of patients (70%, n=14) were between the ages of 2-6, 20% (n=4) were between the ages of 6-10, and 10% (n=2) were between the ages of 10-13. The mean age of the patients was 4.7±3.22, the mean weight was 17.61±7.97 kg, the mean height was 103.38±27.00 cm.

It was observed that 57.1% (n=12) of the patients had a family history of phenylketonuria other than themselves. The majority of patients (70%, n=14) have a kinship relationship between their parents.

The mean blood phenylalanine level, blood tyrosine levels, daily phenylalanine, protein and energy intake level of the patients in 4 controls are shown in Table I.

The mean blood phenylalanine level of the patients was 356.95± 193.18 µmol/L at the first follow-up, 345.55±180.35 µmol/L at the second follow-up, 327.16±213.62 µmol/L at the third follow-up, and 274.77±205.66 µmol/L at the fourth follow-up. When blood tyrosine levels were examined, it was found to be 105.78±188.99 µmol/L in the first control, 59.65±31.24 µmol/L in the second control, 59.36±30.55 µmol/L in the third control, 49.37±17.57 µmol/L in the fourth control.

When the average amount of protein taken by the patients in the daily diet is examined, it is seen that it is 33.86±10.47 g in the first control, 35.01±10.62 g in the second control, 35.26±9.70 g in the third control, 35.47±9.89 g in the fourth control. When the average total energy they received with the daily diet was 1442.07±364.31 kcal in the first control, 1449.67±399.68 kcal in the second control, 1432.38±373.39 kcal in the third control, 1425.09±368.76 kcal in the fourth control. The mean daily dietary phenylalanine level of the patients was 276.09±188.85 mg at the first control, 257.71 ±130.09 mg at the second control, 254.86±174.43 at the third control, and 270.00±158.89 mg at the fourth control. Daily intake of protein, phenyalanine, tyrosine and energy was sufficient according to the recommended daily allowance of patients.

The nutritional habits of patients, including the consumption of amino acid mixtures and special products, as well as the number of main and snack meals, are presented in Table II.

When the daily meal consumption of the patients was examined, it was seen that 95% (n=19) made 3 main meals and 5% (n=1) made 2 main meals. When we look at the snack consumption, 10% (n=2) stated that they had 1 snack, 65% (n=13) had 2 snacks, 15% (n=3) had 3 snacks, 5% (n=1) had 4 snacks, and 5% (n=1) had 5 snacks.

When the number of meals consumed daily of the amino acid mixture used was questioned, it was seen that 20% (n=4) of the patients consumed 1 meal, 45% (n=9) consumed 2 snacks, 5% (n=1) consumed 3 meals, 5% (n=1) consumed 4 meals, 20% (n=4) consumed 5 meals, and 5% (n=1) consumed 6 meals. The amino acid mixture is consumed by 30% (n=6) of the patients with a bottle, 65% (n=13) by a glass and 5% (n=1) by a bowl. When it was questioned whether the daily recommended amount of amino acid mixture was followed, it was learned that 50% (n=10) of the patients always consumed all of them, 40% (n=8) consumed them most of the time, and 10% (n=2) rarely consumed them. When the emotional state of the families was questioned at the time of consumption of the amino acid mixture by the child, 60% (n=12) said that they felt comfortable, 5% (n=1) said that they were calm, 30% (n=6) said that they were nervous, and 5% (n=1) said that they were hectic.

While 60% (n=12) of the patients consumed the amino acid mixture with other individuals, 40% (n=8) did not. Likewise, when the consumption status of the amino acid mixture in kindergarten and/ or school was questioned, it was seen that 50% (n=10) did not consume it. When the reason for not consuming was questioned, 60% (n=6) of the patients stated that they did not consume it because they were ashamed, 20% (n=2) because it was difficult to carry, and 20% (n=2) because they hid their disease.

When the consumption status of special products was questioned, it was stated that 60% (n = 12) of the patients consumed, 40% (n = 8) of the non-consumers and 50% (n = 4) of the products were expensive and 50% (n = 4) of them tasted bad.

When parents were asked about their children's compliance with the diet, 85% (n=17) stated that they complied with the diet and 15% (n=3) stated that they were non-compliant. When the families who stated that there was no compliance with the diet were asked about the reason for this situation, 10% of them stated that the elders of the family were involved in the extended family, and 5% (n = 1) stated that the children did not want/like to diet.

The relationship between blood phenylalanine and tyrosine levels and daily phenylalanine intake is presented separately in Table III.

The relationship between the daily phenylalanine intake and blood phenylalanine level in the first measurement was a moderate negative correlation (r=-0.577) and was found to be statistically significant (p=0.006). The relationship between the daily phenylalanine intake and blood phenylalanine level in the second measurement was a strong negative correlation (r=-0.716) and

Table I: Blood phenylalanine(phe) and tyrosine levels and daily dietary phenylalanine, protein and energy intake of children with PKU

Blood Findings and Food Consumption	1.Control	2.Control	3.Control	4.Control
Blood phe level (µmol/L)*	356.95±193.18	345.55±180.35	327.16±213.62	274.77±205.66
Blood tyrosine level (µmol/L)*	105.78±188.99	59.65±31.24	59.36±30.55	49.37±17.57
Taken daily with diet amount of phenylalanine (mg/day)*	276.09±188.85	257.71±130.09	254.86±174.43	270.00±158.89
Total protein (g/day)*	33.86±10.47	35.01±10.62	35.26±9.70	35.47±9.89
Total Energy (kcal/day)*	1442.07±364.31	1449.67±399.68	1432.38±373.39	1425.09 ±368.76

***:** *mean ± SD*

Table II: Patients' eating habits, amino acid mixture and special product consumption status

	n (%)
Number of main meals consumed per day	
2	1 (5)
3	19 (95)
Number of snacks consumed per day	
1	2 (10)
2	13 (65)
3	3 (15)
4	1 (5)
5	1 (5)
Number of meals consumed daily of the amino acid mixture	
1	4 (20)
2	9 (45)
3	1 (5)
4	1 (5)
5	4 (20)
6	1 (5)
Consumption of amino acid mixture	
With a baby bottle	6 (30)
With glass	13 (65)
With bowl	1 (5)
Consumption of the amino acid mixture in the recommended amount per day	
All the time	10 (50)
Most of the time	8 (40)
Rarely	2 (10)
Consumption of amino acid mixture in the presence of other ındividuals	
Yes, it consumes	12 (60)
No, it does not consume	8 (40)
Consumption status of amino acid mixture in kindergarten/school	
Yes, it consumes	10 (50)
No, it does not consume	10 (50)
The reason why children who do not consume amino acid mixtures in the presence of other ındividuals and in kindergarten/school do not consume	
Ashamed	6 (60)
Difficult to carry	2 (20)
Hides the illness	2 (20)
Special product consumption status	
Yes, it consumes	12 (60)
No, it does not consume	8 (40)
The reason why children who do not consume special products do not consume	
Expensive prices	4 (50)
Bad taste	4 (50)
Families' children's feelings/emotional state during the consumption of amino acid mixtures	
Comfortable	12 (60)
Calm	1 (5)
Nervous	6 (30)
Hectic	1 (5)
According to parents, the compliance status of their children with their current diet	
Yes, it fits	17 (85)
No, it doesn't fit	3 (15)
The reason for non-compliance of patients who are thought to be non-compliant with the diet	
Involvement of family elders in the extended family	2 (10)
Unwilling/disliking dieting	1 (5)

Table III: Relationship between blood phenylalanine and tyrosine levels of children with pku and the amount of phenylalanine taken in the daily diet

Daily intake of phenylalanine	Blood phenylalanine level*	Blood tyrosine level*
1. Control	r=-0.577 p=0.006	r=0.297 p=0.191
2. Control	r=-0.716 p<0.001	r=0.097 p=0.676
3. Control	r=-0.739 p<0.001	r=-0.093 p=0.687
4. Control	r=-0.534 p=0.013	rho=0.088 p=0.704

***:** *1st, 2nd, 3rd, 4th follow-up visits, respectively,* ***r:** Pearson correlation coefficient,* ***rho:** Spearman correlation coefficient*

Table IV: Relationship between blood phenylalanine level and amino acid mixture consumption and diet adherence of children with PKU

Blood phenylalanine level	Consumption of the entire amino acid mixture*	Daily consumption frequency of amino acid mixture, meal consumption*	Compliance with the diet*
1. Control	rho=0.138 p=0.550	rho=-0.011 p=0.962	rpb=-0.267 p=0.242
2. Control	rho=-0.155 p=0.501	rho=-0.108 p=0.641	rpb=-0.225 p=0.326
3. Control	rho=-0.280 p=0.219	rho=-0.014 p=0.953	rpb=0.086 p=0.710
4. Control	rho=-0.231 p=0.314	rho=-0.093 p=0.689	rpb=-0.237 p=0.301

***:** *1st, 2nd, 3rd, 4th follow-up visits, respectively,* ***rpb :** Point double series correlation coefficient,* ***rho:** Spearman correlation coefficient.*

Table V: Relationship between diet adherence and daily consumption frequency of amino acid mixture

	Compliance with the diet	p
Daily meal consumption of the amino acid mixture	Cramer's V =0.667	p=0.025

***Cramer's V:** Cramer's V correlation coefficient*

was found to be statistically significant (p<0.001). The relationship between the daily phenylalanine intake and blood phenylalanine level in the third measurement was a strong negative correlation (r=-0.739) and was found to be statistically significant (p<0.001). The relationship between the daily phenylalanine intake and blood phenylalanine level in the fourth measurement was a moderate negative correlation (r=-0.534) and was found to be statistically significant (p=0.013).

No statistically significant relationship was found between dietary phenylalanine levels and blood tyrosine levels measured in four consecutive controls during follow-up (p=0.191, p=0.676, p=0.687 and p=0.704, respectevily).

The relationship between blood phenylalanine levels and the complete consumption of the amino acid mixture, diet compliance, and the number of daily meals of the amino acid mixture is presented in Table IV.

No statistically significant relationship was found between blood phenylalanine levels and consumption of the amino acid mixture measured in four consecutive controls during follow-up (p=0.550, p=0.501, p=0.219 and p=0.314, respectevily).

No statistically significant relationship was found between blood phenylalanine levels and daily meal consumption of amino acid mixture measured in four consecutive controls during follow-up (p=0.962, p=0.641, p=0.953 and p=0.689, respectevily).

The relationship between diet compliance and the daily meal consumption of amino acid mixtures is presented in Table IV.

The relationship between daily meal consumption of amino acid mixture and dietary adherence was examined with Cramer's V correlation coefficient, and a statistically significant relationship was found at a positive moderate level (Cramer's V=0.667) (p=0.025).

DISCUSSION

In phenylketonuria, a number of barriers such as time, management and economic reasons can make it difficult for both patients and families to comply with the diet, which is the most important step of treatment. Problems in compliance with the diet cause blood phenylalanine levels to rise and this negatively affects long-term neurocognitive development. Considering the positive effects of phenylalanine intake at the recommended level with the diet on the prevention of neurological disorders and the achievement of normal intelligence coefficients by patients, the importance of compliance with the diet emerges (9,10).

In recent studies, it has been emphasized that better metabolic control is achieved by keeping blood phenylalanine levels at lower limits, and it is reported that limit values can be kept higher for adolescence. In our study, the target blood phenylalanine level was determined as 120–360 µmol/L (2-6 mg/dL) for all age groups in order to ensure metabolic control (11,12).

In our study, although the average blood phenylalanine level was found to be between 120-360 µmol/L in all controls of the patients; it is seen in the Table I that the upper level of the standard deviation is well above 360 µmol/L. When the relationship between the phenylalanine level taken in the daily diet and the blood phenylalanine level is considered;A moderate positive correlation was found in the 1st and 4th controls,and a high positive correlation was found in the 2nd and 3rd controls (p=, 0.006, p<0.001, p<0.001, p=0.013). It is thougt that the cause of this situation is due to the deficiencies and errors in the information obtained from the patients' families. If the daily recommended phenylalanine level is followed, it is seen that blood phenylalanine levels remain at the target level and metabolic control is achieved. In the literature, as in our study, there are studies in which blood phenylalanine levels are seen in target ranges with compliance with diet, but there are also studies in which blood phenylalanine values are seen above the target range. In a study conducted on 85 patients diagnosed with phenylketonuria in various age groups, the mean phenylalanine values of the patients were found to be 342 µmol/L in patients under 18 years of age and 440.4 µmol/L in patients over 18 years of age (13). In another study in which 144 children and their mothers were evaluated with phenylketonuria between the ages of 1-15, it was determined that the average blood phenylalanine values of 60.4% of the patients were above the recommended range of 120-360 µmol/L, and dietary compliance was worse in school-age children (5).

When the relationship between daily phenylalanine levels and blood tyrosine levels was examined, no statistically significant relationship was found in all 4 controls (p=0.191, p=0.676, p=0.687, p=0.704). Phenylalanine-free amino acid mixtures provide the other essential amino acids required by the body and sustain growth and development (14).

While 40% of the patients did not want to consume amino acid mixtures with other individuals, 50% stated that they did not consume them at school. When the reason for not consuming was questioned, answers such as embarrassment, not wanting to carry, and hiding one's illness were received. Similarly, studies show that children have taste and flavor problems while consuming amino acid mixtures, and they do not want to consume them for reasons such as not needing them at school and being embarrassed (15,16).

When the number of daily meals taken with amino acid mixture and diet compliance parameters (such as blood PHE level) were examined, a positive moderate statistically significant relationship was found (p=0.025). As the number of meals taken with amino acid mixture during the day increases, diet Phe level remains within target ranges and fluctuations in blood Phe level are prevented. It is observed that compliance increases. In a study conducted on 41 patients between the ages of 8 and 19 with phenylketonuria, it was observed that consuming amino acid mixtures at least three meals provided better metabolic control (17). With the advancement of age, the number of daily meal consumption of the amino acid mixture decreases in children, which makes it difficult to comply with the diet (16). There are studies showing that dividing amino acid mixtures into at least 3-4 meals during the day prevents fluctuations in blood phenylalanine levels (18).

When the relationship between blood phenylalanine level and consumption of the entire amino acid mixture (p=0.550, p=0.501, p=0.219, p=0.314), blood phenylalanine level and compliance with diet (p=0.242, p=0.326, p=0.710, p=0.301), blood phenylalanine level and the number of daily meals consumed of the amino acid mixture (p=0.962, p=0.641, p=0.953, p=0.689), no statistically significant relationship was found in all 4 controls.

In 40% of patients who do not consume special products, the reasons for not consuming them are that the products are expensive and taste bad. When we look at the literature, in parallel with our study, among the reasons why special products are not consumed, are that they taste and smell badly, and at the same time they are high cost (8,19).

When parents were asked about their children's level of compliance with the diet, 85% said that they followed the diet, while 15% said that they were non-compliant with the diet; As a reason, they stated that the family elders in the extended family interfered and that their children did not want and did not like to diet. Studies have shown that patients' social lives and ages are related to their compliance with diet. It is stated that each age group and social life should be evaluated within itself, and the effect of mood changes on diet should not be ignored (20-22).

In our study, when the emotional state of the families was questioned during the consumption of amino acid mixtures by the child during the day, 60% stated that they were relaxed, 5% were calm, 30% were nervous, and 5% were hectic. In a study conducted on the parents of 36 healthy children with 61 phenylketonuria and a control group, it was shown that the mothers of children with phenylketonuria had higher anxiety levels and depression scores than the control group. Studies have shown that the tension between parents in child care makes it difficult to comply with the diet (23). It has been emphasized that with the provision of education plans for parents about the disease, compliance with diet and diet success will increase in patients with phenyleketonuria (24).

CONCLUSION

Phenylketonuria is one of the hereditary metabolic diseases for which medical nutrition therapy is of great importance. With early diagnosis and treatment, it should be ensured that a nutritional therapy that is limited from natural proteins, amino acid mixtures and artificial proteins, and adequate energy intake is provided for life. Many factors such as the age of the patients, their presence in the school age period, the variability of their eating habits with age, living in a large family, and intervening recurrent infections make it difficult to adapt to diet and metabolic control. For this reason, it should not be forgotten that there are multiple parameters at the point of providing metabolic control and each of them also affects the process of adaptation to the diet.

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Original Article

Evaluation of Infants Hospitalized in Intensive Care Unit Due to Acute Severe Bronchiolitis in Terms of Recurrent Wheezing or Asthma Development

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ABSTRACT

Objective: Bronchiolitis stands out as the most prevalent lower respiratory tract infection among young children.Severe bronchiolitis, or bronchiolitis requiring admission to the hospital, affects 2-3% of all infants. The aim of this study was to evaluate individuals who were followed up in the pediatric intensive care unit (PICU) due to severe bronchiolitis in terms of asthma development.

Material and Methods: Patients who were admitted Ankara Bilkent City Hospital PICU between January 2013 and December 2022, who were diagnosed with severe bronchiolitis and who had no additional systemic disease were included in the study. Demographic and clinical characteristics of patients, intensive care support treatments, duration of hospital stays, atopic conditions, and respiratory viral panel cultures was documented. The current clinical condition of the patients was documented through hospital records and telephone interviews conducted with their caregivers. The existence of asthma symptoms and the utilization of treatments within the last 12 months were evaluated according to the guidelines of the Global Initiative for Asthma (GINA) and the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire.

Results: The mean age of the 60 patients admitted to the intensive care unit who met the study criteria was 13.5±7.2 months. The mean age of the children at the time of the study was 42.5 months. Male gender was more predominant (n=39, 65%). The mean number of days that respiratory support was received in intensive care was 4.9 (±3.5) days and the mean number of days of systemic steroid therapy was 3.8 (±1.7) days. In the viral respiratory tract, Respiratory Syncytial Virus (RSV) was isolated at the highest frequency in 27 patients, accounting for 45%, followed by rhinovirus (n=6, 10%) and Bocavirus (n=5, 8.3%). The number of patients receiving current asthma treatment was (n=33, 55%). Upon assessing the current status, it was found that there had been 25 (41.6%) patients with asthma attacks over the past 12 months.

Conclusion: This study revealed that over half of the patients who experienced severe bronchiolitis subsequently developed asthma, with some not being referred to an allergy clinic. Furthermore, it was observed that certain patients, despite presenting with asthma symptoms, were unaware that these symptoms were attributable to asthma. We recommend that patients admitted to the PICU with a diagnosis of severe bronchiolitis be closely monitored for the potential development of asthma and that families be thoroughly informed at the time of discharge.

Keywords: Asthma, Infants, Pediatric Intensive Care, Severe Bronchiolitis, Wheezing

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

Ethics Committee Approval: This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Bilkent City Hospital Ethics Committee (27.03.2024/118).

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INTRODUCTION

Bronchiolitis stands out as the most prevalent lower respiratory tract infection among young children. Almost all children are exposed to viral agents during the first two years of life. Severe bronchiolitis, or bronchiolitis requiring admission to the hospital, affects 2-3% of all infants, and of these, 3-11% require admission to the (PICU) (1-3). There is a lack of extensive data in the existing literature concerning the relationship between experiencing severe bronchiolitis in infancy and its impact on the development of recurrent wheezing or asthma later in life (4).

Asthma is a heterogeneous disease characterized by chronic airway inflammation. Asthma is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation. Asthma affects 1-18% of the population in different countries (5). According to the modified International Study of Asthma and Allergies in Childhood (ISAAC) study conducted in Turkey, the cumulative prevalence of childhood asthma was found to be between 13.7-15.3% (6). Families are most concerned about the risk of wheezing children developing asthma later in life. Currently, there is no definitive laboratory test that can predict which wheezing children will develop asthma. Real-life data on the proportion of severe bronchiolitis cases that progress to wheezing infant and/or asthma are limited. The primary objective of our study was to ascertain the rates of recurrent wheezing and the development of asthma during the follow-up period for children who were hospitalized in the PICU with a diagnosis of severe bronchiolitis.

MATERIALS and METHODS

The study included patients admitted to Ankara Bilkent City Hospital PICU between January 2013 and December 2022 who were diagnosed with severe bronchiolitis within the first 24 months of life, according to the classification outlined in the Turkish Thoracic Society Diagnosis and Treatment Consensus Report (7). Patients with a prior diagnosis of wheezing infant syndrome and those with additional systemic chronic diseases were excluded from the study. Patients' demographic characteristics, intensive care support treatments, duration of hospital stays, atopic conditions, and respiratory viral panel cultures have been recorded. Medical records of the patients were evaluated for follow-up results. The current clinical status of the patients was recorded by telephone interviews conducted by the caregivers, with the interviews being carried out by the researchers themselves. The presence of asthma symptoms and the use of treatment in the last 12 months were assessed using the Global Initiative for Asthma (GINA) guidelines and the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire. The control status of those with asthma was also evaluated using the GINA asthma control questionnaire. The prevalence of asthma was investigated using the ISAAC questionnaire, validated in Turkish (8, 9). The primary questions include "wheezing in the past 12 months," "history of asthma," and the presence of symptoms within the past 12 months. "four or more attacks of wheezing," "cough with no cold or respiratory infection," "sleep disturbed due to wheezing ≥1 night per week," "wheezing due to exercise," and "speech limited due to wheezing." Four additional questions were included to investigate the severity of asthma and use of medications: "number of asthma attacks in the last 12 months," "attendee in emergency service in the last 12 months because of asthma," "hospitalization in the last 12 months due to asthma," and "daily use of medications used to treat asthma". Factors that could pose a risk for the development of recurrent wheezing or asthma were assessed, including gender, multiple intensive care hospitalizations, duration of active intensive care treatment, mechanical ventilation, total length of hospitalization, eosinophil percentage, presence of atopy, presence of RSV infection, birth weight, and delivery method. The recorded respiratory viral panel results for the patients were obtained through the application of PCR techniques.

Statistical analysis

All statistical analyses were performed with the SPSS 25.0 program (IBM Corp, Armonk, NY). Categorical variables were expressed as frequency and percentage. Continuous data that demonstrated a normal distribution were presented as mean and standard deviation. Logistic regression analysis was conducted to evaluate the independent effects of variables on asthma development. A p value of <0.050 was considered statistically significant.

RESULTS

The mean age of the 60 patients admitted, who met the study criteria, was 13.5±7.2 months. Male gender was more predominant (n=39, 65%). The mean follow-up period after discharge for the patients was 34.5±20.2 months. The mean age of the children at the time of the study was 42.5 months. The mean number of days that respiratory support was received in intensive care was 4.9 (±3.5) days and the mean number of days of systemic steroid therapy was 3.8 (±1.7) days, details in Table I. It was observed that 21.7% (n=13) of the patients experienced an episode requiring intensive care admission following a severe bronchiolitis attack. Among respiratory supports, the number of patients receiving invasive treatment, including Noninvasive Mechanical Ventilation (NIMV), High-Frequency Oscillatory Ventilation (HFOV), and Intubation, was a total of 52 (86.7%) (Table I). Total of 32 (53.3%) patients receiving magnesium treatment and 31 (51.7 %) ipratropium bromide treatment. In the respiratory viral panel results, pathogens were isolated in 42 patients. Among these, the most frequently isolated viruses were respiratory syncytial virus (RSV) in 27 patients, followed by rhinovirus (6, 10%) and bocavirus (2, 3.3%) (Table II). During the follow-up, 23 (38.3%) patients were admitted to the pediatric allergy outpatient clinic.

Patients were questioned according to the ISAAC asthma questionnaire for the last 12 months and the details are given in table III. The number of patients receiving current asthma treatment was 33 (55%). Upon assessing the current status, it was found that there had been 25 (41.6%) patients with asthma attacks over

Table I: The characteristics of PICU admission and treatment

Follow-up period from discharge (month)*	34.5±20.2 (16-108)
Number of intensive care admissions*	1.3±0.84 (1-6)
Intensive care effective treatment time (day)*	4.9±3.5 (1-20)
Steroid treatment time (day)*	3.8±1.7 (0-9)
Total duration of admission (day)*	10.6±8.7 (1-66)
Receiving treatment†	
Magnesium treatment	32 (53.3)
Ipratropium Bromide treatment	31 (51.7)
Free flow oxygen delivery	2 (3.3)
Nonrebreathing mask	6 (10)
HFOV	37 (61.7)
NIMV	6 (10)
Intubation	9 (15)

***:** *mean±standart deviation (minimum-maximum),* **†:** *n(%),* ***HFOV:** *High-frequency oscillation ventilation,* ***NIMV:** *Non-invasive mechanic ventilation*

Table II: Respiratory viral panel results

RSV*	27 (45)
Rhinovirus*	6 (10)
HboV*	5 (8.3)
Adenovirus*	2 (3.3)
nCoV2*	2 (3.3)

***:** *n(%),* ***RSV:** *Respiratory syncytial virus,* ***HboV:** *Bocavirus,* ***nCoV2:** *Novel Coronavirus*

Table III: ISAAC Asthma Questionnaire

	Yes*
Wheezing in the last 12 months	25 (41.7)
Asthma attacks in the last 12 months 1-3 attacks 4-12 attacks	22 (36.7) 3 (5)
Wheezing due to exercise	20 (33.3)
Speech limited due to wheezing	12 (20)
Cough without cold or respiratory infection in the last 12 months	13 (21.7)
Sleep disturbance due to wheezing	18 (30)
Emergency room attendee due to asthma	20 (33.3)
Hospital admission due to asthma	11 (18.3)
Using steroids for asthma in the last 12 months	8 (13.3)
Using bronchodilators for asthma in the last 12 months	36 (60)
Current asthma treatment	33 (55)
Physician diagnosed asthma†	34 (56.7)

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

the past 12 months (Table III). Out of the 34 patients diagnosed with asthma, 17 were being followed with an asthma diagnosis at our clinic; however, the diagnosis of the remaining 17 patients was determined through phone interviews. In the present study, we sought to examine the potential influence of various factors

Table IV: Analysis table of risk factors for the development of asthma

	Univariate		
	OR	CI	p
Gender	1.17	0.4-3.41	0.765
Multiple intensive care admissions	2.15	0.58-7.98	0.25
Effective treatment duration (days)	0.95	0.82-1.1	0.572
Mechanıcal Ventılatıon	1.56	0.48-5.06	0.45
Total hospitalization duration	0.94	0.82-1.07	0.35
Percentage of eosonophils	1.03	0.77-1.4	0.8
Presence of atopy	0.59	0.05-6.95	0.68
RSV isolation	1.65	0.59-4.63	0.33
Birth weight	0.98	0.27-3.57	0.98
Delivery method	0.94	0.33-2.66	0.91

on the development of asthma following intensive care unit (ICU) admission. Our investigation encompassed a range of variables, including gender, the necessity for multiple PICU admissions, the duration of active treatment, the use of mechanical ventilation, eosinophil percentage, the presence of atopy, RSV isolation, mode of delivery, and birth weight. However, our analysis did not identify any statistically significant risk factors (Table IV).

DISCUSSION

The number of patients with asthma with a current doctor's diagnosis was 34 (56.6%), and the number receiving current treatment was 33 (55%). According to the ISAAC questionnaire, 25 (41.6%) patients had wheezing attacks in the last 12 months. Early-life viral respiratory infections have been linked to an elevated risk of developing recurrent wheezing and asthma (10, 11). Bronchiolitis is the most prevalent acute lower respiratory tract infection during infancy. Despite the majority of cases being mild to moderate, some children may experience severe symptoms necessitating hospitalization. Severe bronchiolitis significantly increases the risk of long-term respiratory issues; in fact, approximately 30–40% of hospitalized infants with bronchiolitis will later develop recurrent wheezing or asthma. However, the factors determining which infants will develop chronic respiratory conditions are not fully understood (12-14). The findings of our study indicate that the incidence of asthma development following severe bronchiolitis is comparable to that observed in the aforementioned studies. The factors influencing the development of asthma in infants with bronchiolitis remain ambiguous; our study aimed to assess the impact of bronchiolitis severe enough to necessitate PICU hospitalization on the subsequent development of asthma. In our study, when we evaluated 60 patients who were hospitalized for intensive care and questioned their current status with the ISAAC asthma questionnaire. The number of patients with asthma with a current physician diagnosis was 34 (56.6%) and 17 (28.3%) patients continue to be followed up with a diagnosis of asthma in our clinic. Since the diagnosis of 17 patients was based on their

answers to the ISAAC questionnaire. This rate was found to be high compared to the prevalence of asthma in our country (6, 9, 15-19)

Exacerbations play a crucial role in asthma, exerting a substantial impact on both the child and their family. In our study, when we asked the patients about asthma attacks in the last 12 months, we found that the number of patients who experienced an asthma attack in the past year was 25 (41.7%), and among these patients, three (5%) had experienced more than three attacks. Looking at surveillance studies conducted in the literature, the incidence of asthma attacks has been found to be approximately between 30-40% (20, 21). A survey of 753 children with asthma in seven European countries revealed that 36% of children require an unscheduled urgent care visit in the past 12 months (22). Engelkes et al. (23) determined the rate of asthma attacks in the asthma cohort observed in the last 1 year to be 25%.

When examining asthma prevalence studies conducted in Turkey using the ISAAC questionnaire, Topal et al. (15) reported the prevalence of wheezing in the last 12 months at 12.3%. In other prevalence studies conducted in different regions of our coutry, the wheezing prevalence in the last 12 months was determined as follows: Çelik et al.(18) reported 23.2%, Cetemen et al. (17) 19.3%, Ece et al. (16) 14.7% and Kalyoncu et al. (19) 11.9%. When we look at the prevalence studies conducted in different regions in our country, we found that the prevalence of wheezing in the last 12 months in the follow-up of patients with a history of intensive care unit hospitalization due to severe bronchiolitis was 41.7% in our study, which is approximately two times more frequent than the study with the highest prevalence. Therefore, if the patient is hospitalized in PICU due to severe bronchiolitis even once, the risk of wheezing will increase in the future. In other recent studies, it has been found that the rate of asthma development during intensive care unit hospitalizations for severe bronchitis is higher than in non-admitted patients (24, 25).

Some studies have found that approximately 10% to 20% of patients requiring hospitalization for bronchiolitis require intensive care support (26-28). However, when we compared the patients who received only oxygen therapy with those who received invasive respiratory support, we did not find a significant difference between them (p=0.795). Sonnaville et al. (24) evaluated 74 patients who required mechanical ventilation only because of severe bronchiolitis and found that the rate of current asthma development during follow-up was approximately 15% and stated that having severe bronchiolitis requiring mechanical ventilation poses a risk for future asthma development.

In our study, when examining the agents contributing to the development of bronchiolitis, RSV was identified as the most prevalent (n=27, 45%), followed by rhinovirus (n=6, 10%) and bocavirus (n=5, 8.3%). Likewise, in our exploration of bronchiolitis etiologies in the literature, the predominant findings across numerous studies revealed the prevalence of RSV, followed by rhinovirus (29-32). Examining the respiratory viral panel results in individuals who experienced wheezing attacks in the last 12 months revealed that RSV was isolated in the first place with a rate of 43.5%. In our study, RSV was the most frequently isolated virus with a rate of 45%. Many studies have been conducted on the relationship between RSV and the development of asthma. Also many long-term follow-up studies have shown that RSV-induced bronchiolitis is associated with the later development of asthma (33, 34). Recent literature data have demonstrated that Bocavirus infections have a tendency to manifest as severe cases, requiring prolonged respiratory support for affected patients (35-37). Corresponding data supporting this information are available in the literature (38). However, in our study, we did not observe a statistically significant difference, and we attributed this to the possibility that Bocavirus was isolated from only 5 patients in the sample.

More studies are needed to say with certainty that admission of children in the PICU for severe bronchiolitis increases the risk of asthma in the future. However, caregivers should be informed of the high likelihood of wheezing and obstructive pulmonary disease at any stage of life. Therefore, it is important to monitor and evaluate children for the development of asthma.

CONCLUSION

In this study, more than half of the patients with severe bronchiolitis developed asthma and some patients were not referred to the allergy clinic. In addition, although some patients had asthma symptoms, they were unaware that these symptoms were caused by asthma. We suggest that patients hospitalized in PICU with a diagnosis of severe bronchiolitis should be closely followed up in terms of asthma development and families should be informed at discharge.

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Original Article

Clinical Findings and Outcome of Moyamoya Disease/Syndrome

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ABSTRACT

Objective: Moyamoya disease is a rare progressive cerebrovascular disorder. It is characterized by progressive stenosis in the terminal branches of the internal carotid arteries, leading to the formation of an abnormal vascular network. The aim of this study was to present the clinical findings and outcomes of pediatric patients diagnosed with Moyamoya disease by analyzing our cohort to identify the common clinical presentations, diagnostic challenges, and treatment outcomes associated with this rare cerebrovascular disorder.

Material and Methods: Nine pediatric cases of Moyamoya disease admitted over a 10-year period were retrospectively reviewed. Clinical presentations, associated diseases, radiological findings, treatments, and outcomes were analyzed.

Results: The median age at diagnosis was 48 months (3-87). Presenting symptoms included hemiparesis in five patients, seizures in six patients, headache in one patient, and choreathetosis with headache in one patient. Three patients experienced symptoms triggered by fever, and one patient by exposure to hot water. Seven patients presented with ischemic symptoms, while two presented with non-ischemic symptoms. Neurofibromatosis type-1 (NF-1) was associated with the disease in four patients. Recurrent attacks occurred in two patients. Interictal electroencephalograms (EEGs) showed hemispheric/focal slowing in five cases. Cranial magnetic resonance imaging (MRI) revealed infarctions in seven patients, and MR angiography showed bilateral findings in six patients. Two patients experienced no long-term sequelae.

Conclusion: Moyamoya disease manifests with both ischemic and non-ischemic symptoms. Recognition of non-ischemic presentations requires a high index of suspicion for accurate diagnosis.

Keywords: Children, Electroencephalogram, Moyamoya disease, Neuroimaging, Stroke

INTRODUCTION

Moyamoya disease (MMD) is a rare chronic cerebrovascular condition of unknown etiology. The disease is particularly prevalent in East Asian populations, with a higher incidence in Japan, Korea, and China compared to Western countries. In Japan, the annual incidence is estimated to be between 0.35 and 0.94 per 100.000 individuals. The peak onset typically occurs in children between 5 and 10 years of age. The disease is characterized by progressive occlusion or narrowing of the supraclinoid internal carotid artery and its major branches in the circle of Willis, usually bilaterally and idiopathically. Patients may present with recurrent ischemic or hemorrhagic strokes, as well as non-ischemic manifestations (1).

Moyamoya disease is referred to as moyamoya syndrome (MMS) when it co-occurs with another clinical condition such as neurofibromatosis type-1, genetic disorders (e.g., trisomy 21, Williams syndrome, PHACE syndrome), sickle cell disease, among others (2). The presence of familial cases and regional disparities in epidemiological data suggests a genetic component in its pathogenesis.

There are extensive series on moyamoya disease in the literature, with many studies originating from regions like Japan where the prevalence is high. Some of these studies include both adult and pediatric patients. However, in our country, it is rarely seen. We aimed to contribute to the literature by presenting our cohort, which, despite the small number of patients, includes a young age

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

Ethics Committee Approval : This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Karadeniz Technical University, Faculty of Medicine, Clinical Research Ethics Committee 2023/173 - 10.03.2023.

***Contribution of the Authors*: DİLER DURGUT B, DİLBER B, AMAŞAK T, AHMET SARI and CANSU A:** contributed to the medical care and diagnose for this study. All authors contributed to idea design, data collection and writing article stages.

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group and a high proportion of patients with Neurofibromatosis type 1 (NF1), as well as diverse clinical presentations.

MATERIALS and METHODS

Patients diagnosed with moyamoya disease/syndrome in the pediatric neurology outpatient clinic between 2013 and 2023 were included in the study. All patients with a diagnosis confirmed by clinical and imaging findings were enrolled. Patients with insufficient data or follow-up duration were excluded from the study.

Demographic data such as age, gender, and age at diagnosis were recorded from hospital charts. The presenting complaints, neurological examination findings, clinical symptoms, concomitant diseases of the patients were documented in detail. Brain MRI, magnetic resonance angiography (MRA), and other relevant imaging results were reviewed and recorded. Surgical interventions (e.g., revascularization surgeries), medical treatments were detailed. The clinical course, prognosis, complications, and outcomes during the follow-up period were recorded.

Diagnostic delay was defined as cases diagnosed at least one year after the initial presentation.

The study was approved by Karadeniz Technical University, Faculty of Medicine, Clinical Research Ethics Committee 2023/173 - 10.03.2023.

Statistics:

Data analysis was performed using the Statistical Package for the Social Sciences version 23 (SPSS Inc., Armonk, NY, IBM Corp., USA) software. Numerical data were expressed as median (min-max) and categorical variable as number and percentage

RESULTS

Nine patients were diagnosed with Moyamoya disease/syndrome (MMD/MMS). None of the patients had a family history of Moyamoya, and there was no consanguinity between the parents. The median age at diagnosis was 48 months (3-87). Diagnostic delay was observed in three patients. The male-to-female ratio was 2:1. Seizures were observed in five patients, hemiparesis in five patients, headache in one patient, and headache with choreoathetosis in one patient. One of the cases presented with status epilepticus. Symptoms were triggered by fever in three patients and exposure to hot water in one patient. MMS was associated with neurofibromatosis type 1 in four patients. Recurrence occurred in two patients. MMD/MMS was bilateral in five patients and unilateral in three patients initially. Disease progression to bilateral involvement was observed during follow-up in one patient initially diagnosed with unilateral disease. Interictal EEGs showed hemispheric slowing in six cases. Baseline thrombophilia tests (anticardiolipin antibodies, factor V Leiden mutation, prothrombin II mutation, homocysteine, Protein C, protein S) were negative in all patients. All patients received aspirin therapy, with one patient additionally receiving fraxiparine. Direct revascularization procedures were performed in two patients. No sequelae were observed in two patients. Genetic testing revealed a positive result for a mutation in the RNF213 gene in one patient, while genetic analysis was not conducted for the other patients. The results are presented in Table I.

In our series, there was only one patient who presented with a movement disorder. This case initially experienced migraine-like headaches for six months, which resolved spontaneously. However, one year later, an 8-year-old boy presented with a two-week history of involuntary movements in his upper extremities. General physical examination revealed no abnormalities, and neurological examination showed bilateral involuntary, brief, irregular, and wavering movements, predominantly in his upper extremities. There was no history of drug therapy or family history of similar conditions. Laboratory studies, including routine blood count, blood amino acids, urine acids, electrocardiogram, chest radiography, tests for collagen vascular disease, renal function, liver function, and coagulation tests, were all normal. Echocardiography showed normal findings. Baseline thrombophilia tests were negative. A heterozygous mutation of the MTHFR gene was identified. On imaging, axial Fluid-Attenuated Inversion Recovery (FLAIR) images revealed high signal intensity at the sulci, known as the 'ivy sign,' and axial contrast-enhanced T1-weighted images showed diffuse leptomeningeal-sulcal enhancement (Figure 1-2). Time-of-flight (TOF) MRA demonstrated multiple tortuous dilated collateral vessels, characteristic of 'moyamoya vessels (Figure 3). Contrast-enhanced MRA maximum intensity projection (MIP) images of bilateral cervical and petrous segments of the internal carotid arteries revealed diffuse narrowing, more pronounced on the right side. Bilateral occlusion of the cavernous and clinoid segments of the internal carotid artery was observed (Figure 4). Following this finding, genetic testing was requested, which identified a heterozygous variant, RNF213 c.12037G>A (p.D4013N) (p.Asp4013Asn). This variant has been previously documented and is listed in the HGMD database as associated with Moyamoya disease. Furthermore, it is classified in the ClinVar database as highly likely pathogenic. Treatment with acetylsalicylic acid rapidly resolved the choreic movements, and no recurrence was observed thereafter. Cranial MRI findings revealed evidence of infarction in seven patients, consistent with the ischemic events associated with Moyamoya disease/syndrome (Figure 5).

DISCUSSION

MMD is a rare chronic cerebrovascular occlusive disorder with a multifactorial inheritance pattern, although its exact etiology remains unknown. The primary manifestation of the disease is cerebral ischemia. Transient ischemic attacks (TIAs) can be triggered by events such as hyperventilation, dehydration, fever, and crying in infants, leading to reduced cerebral blood flow (3). In our cohort, presenting symptoms were triggered by fever in three patients and by exposure to hot water in one patient. Fever is the most commonly reported trigger in the literature (4). Therefore, MMD should be considered in cases of TIAs triggered by hyperventilation, dehydration, fever, and crying, highlighting the

Table I: Clinical findings

Case Number	Gender Age (m)	DA (m)	FP (m)	Trigger	Sympton on presentation 1./2./3.	Treatment	AC	R	GMFCS	Outcome	Genetic RNF213	EEG	MRI 1./2./3. a	Angiography
1	M/4	4	24		Left hemiparesis	Aspirin, AE, IR	-	-	3	Hemiparesis NCF	-	N	Brush sign, Infarct	Bilateral ICA occlusion
2	M/8	8	46	f*	Left focal seizure, febril status	Aspirin, AE	NF-1	-	N	No sequelae	-	Right hemisferic slowing	Infarct	Right MCA occlusion
3	F/3		36	f	Seizure, status Hemiparesis	Aspirin, AE	-	-	2	Hemiparesis NCF	-	Right CTO slowing	Infarct	Bilateral ICA stenoz
4	F/24	54	68	hw	Headache, seizure	Aspirin, AE	NF-1	-	1	Mild ID	-	Right hemisferic slowing	-	Right ICA; MCA ACA stenosis
5	F/30	48	48	f	Febril seizure/ seizure and aphasia	Aspirin	NF-1	2	3	Hemiparesis Mild ID	-	N	Brusch sign, Infarct/Infarct	Right ICA, MCA ,PCA occlusion, Right ACA stenoz Then Bilaretal ICA MCA stenosis
6	F/48	48	42	-	Seizure, Right Hemiparesis	Aspirin, AE, IR	NF-1	-	2	Hemiparesis Mild ID	-	N	IVY sign, Infarct	Bilateral ICA stenosis
7	M/84	87	80	-	Headache Choreatethosis	Aspirin	-	-	N	No sequelae	+	N	IVY sign	Bilateral ICA stenosis
8	F/48	48	26	-	Right hemiparesis	Aspirin, Fraxiparine	-	-	3	Hemiparesis NCF	-	Left FC slowing	Infarct	Left ICA stenoz
9	F/48	48	38	-	Seizure, right hemiparesis / seizure/seizure	Aspirin	-	3	5	Tetraparesis Severe MR Exitus	-	Left TPO slowing	İnfarct/ Infarct/ Infarct	Bilateral ICA, MCA stenosis

AC: *Associated condition,* ***AE:*** *Antiepileptic,* ***CTO:*** *Centro-temporo-occipital,* ***DA:*** *Diagnose age,* ***F:*** *Female,* ***FC:*** *Fronto-central,* ***FP:*** *Follow up period,* ***f:*** *Fever,* ***P:*** *Patient,****H:*** *Hemisferic,* ***hw:*** *Hot Water,* ***ICA:*** *Internal carotid artery,* ***IR:*** *Indireck revascularation,* ***ID:*** *Intellectual Disability,* ***M:*** *Male,* ***MCA:*** *Middle cerabral artery,* ***m:*** *months,* ***N:*** *Normal,* ***NCF:*** *Normal Cognitive Functioning,* ***NF-1:*** *Neurofibromatosis type-1,* ***PCA:*** *Posterior cerebral artery,* ***R:*** *Recurrence,* ***S:*** *Sex,* ***TPO:*** *Temporo-parieto-occipital*

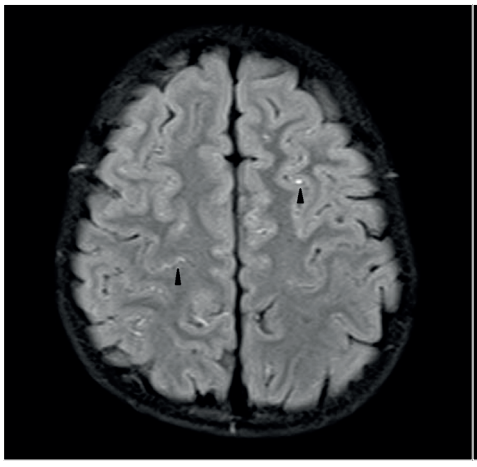

Figure 1 : Axial FLAIR image shows high signal intensity at sulci called 'ivy sign' (black arrowheads) (Case 7).

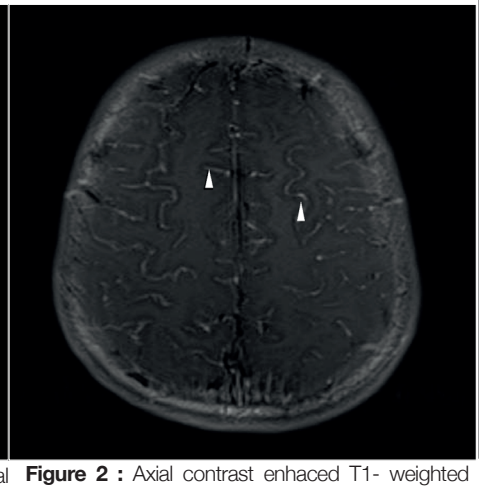

Figure 2 : Axial contrast enhaced T1- weighted image at same level shows diffuse leptomeningeal-sulcal enhacement (white arrowheads) (Case 7).

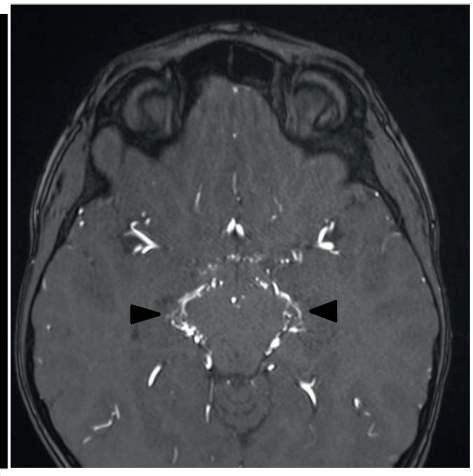

Figure 3 : TOF (time of flight) MRA shows the multiple tortuous dilated collateral vessels called 'moya moya vessels' (arrowheads) (Case7).

importance of recognizing and managing these potential triggers in clinical practice.

The mean age at diagnosis of MMD has been reported between 5.4 and 10.1 years in previous studies (5-7). In our series, the age at diagnosis was lower, with a mean of 38.6 months (3-87). This difference is a significant aspect of our study, possibly attributed to the inclusion of patients with very early symptom onset and a high rate of presentation with hemiparesis, facilitating prompt diagnosis. Three patients were diagnosed before the age of one; two presented with status epilepticus, and one with hemiparesis. Seizure control was achieved with levetiracetam in these patients. One of these patients presents with hemiparesis, while both exhibit no significant impairments in cognitive function. Consistent with findings in the literature, female predominance was observed (8,9).

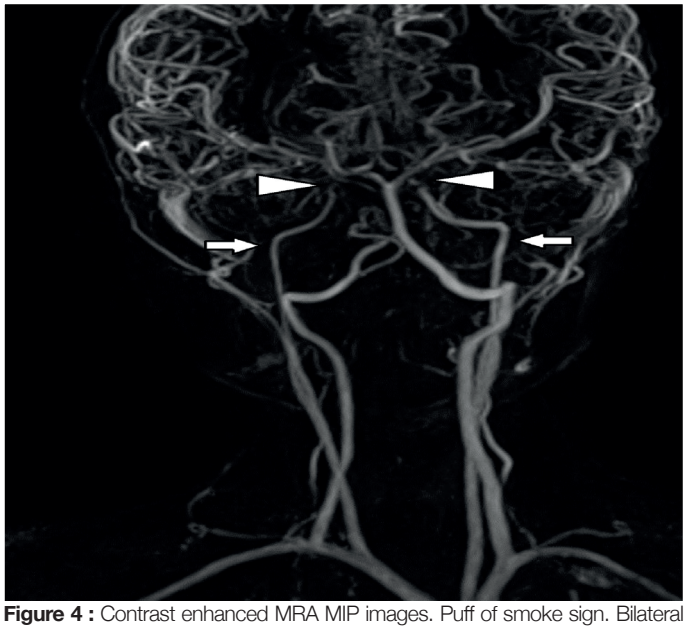

Figure 4 : Contrast enhanced MRA MIP images. Puff of smoke sign. Bilateral cervical and petrous segments of internal carotid arteries show diffuse narrowing more obvious at right (white arrows). Bilateral cavernous and clinoid segments of ICA are occluded (white arrowheads) (Case 7).

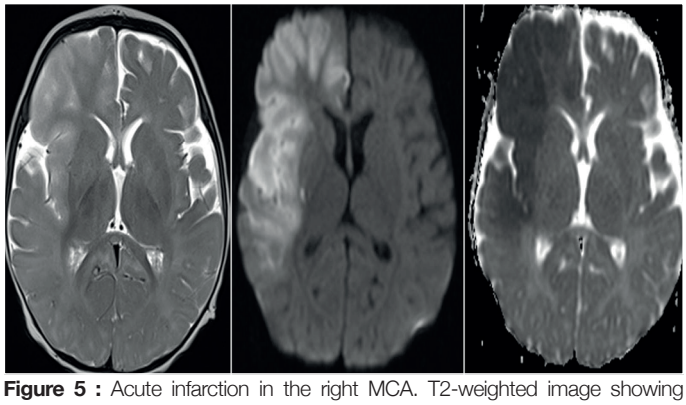

Figure 5 : Acute infarction in the right MCA. T2-weighted image showing hyperintensity. DWI showing restricted diffusion and ADC map showing low signal, confirming restricted diffusion (Case 6).

In the current study, diagnostic delay was observed in three patients (22.2%) with NF-1. This delay can be attributed to nonischemic symptom presentations in two patients and the initial manifestation of a febrile seizure in one patient. Delayed or incorrect diagnoses have been documented in various series investigating MMD. For instance, Graf et al. (10) reported a diagnostic delay exceeding one year in 55.2% of their 192-case series. The relatively low rate of diagnostic delay in our study may be attributed to the small sample size and the predominant presentation of infarction in most cases.

While MMD predominantly presents with hemorrhagic strokes in adults, it more commonly manifests as TIAs or ischemic strokes in children (11-13). Jung et al. (14) reported that acute ischemic infarcts were more frequent in children under 5 years of age, typically showing a gyral pattern, whereas hemorrhagic infarcts were more prevalent in adolescents. In our series, the most frequent clinical presentation was hemiparesis associated with ischemic infarction, with one patient presenting with TIA (Figure 5). In a study by Yoko Sato et al. (15) in Japan, TIAs were the most common clinical presentation (52.11%), followed by infarctions (26.6%). Similar rates were reported in a Chinese series, with TIAs at 48.8% and infarctions at 20.5% (6). In an Italian series, the rates were 26% for TIAs and 29% for infarctions. These regional differences in clinical presentation suggest variability in disease manifestation. Our study was limited by the small number of cases, which may have influenced the observed clinical patterns.

Patients with MMD may also present with non-ischemic manifestations such as headache and choreoathetosis (1). Some patients are incidentally diagnosed (16,17). In our study, two patients presented with headache, one of whom developed choreoathetosis one year after the initial headache. Tomohito et al. (8) reported that approximately 20% of MMD patients experience symptomatic headaches, which are more prevalent in pediatric and young populations. Migraine-like headache is a common symptom in MMD, potentially attributed to chronic hypoxemia in pediatric patients (8,18-21). Furthermore, cortical ischemia often leads to the frequent occurrence of epilepsy among pediatric patients, with five of our patients receiving antiseizure medication.

Presentation with movement disorders is rare in MMD and typically results from basal ganglia damage (18,22-25). The frequency of movement disorders in MMD is estimated to be between 3% and 6% (5,22). Cerebral ischemia is a recognized cause of movement disorders in MMD, with chorea being the most prominent symptom, along with choreo-athetosis, dystonia, limb-shaking, epilepsia-partialis continua, paroxysmal dyskinesia, hemidystonia, and hemichoreoathetosis also observed (8,11). These conditions are thought to arise from ischemic events affecting specific brain areas, particularly the basal ganglia and thalamocortical regions. In our case of chorea presentation, MRI did not reveal any ischemic changes. This clinical condition likely results from vascular bed inadequacy and cerebral hypoperfusion. Hara et al. (26) demonstrated microstructural damage in normal-appearing brain parenchyma using neurite orientation dispersion and density imaging, suggesting that symptoms in our patient may stem from such microstructural changes in the basal ganglia. Chorea is uncommonly seen as an initial presentation of MMD. Despite our study's small sample size, the coexistence of rare presentations represents another notable aspect of our series.

The diagnostic criteria for Moyamoya disease were updated in 2021, resulting in the abolition of the bilaterality rule and the terms "definite case" and "probable case" from the MRI and MRA criteria (18). In the revised criteria, the entity known as Moyamoya syndrome is recognized in the presence of associated conditions such as Down syndrome, brain tumors, and meningitis. In our study, Moyamoya syndrome was diagnosed in four patients due to their association with NF-1.

Gatti et al. (27) reported stroke occurrence in 11% of 11 patients with NF-1 in their study focusing on stroke rates according to different etiologies. In our study, stroke developed in three out of four patients with NF-1, as well as in three out of four patients without any associated conditions. Larger series are necessary to comprehensively assess the clinical presentation and prognosis based on different etiologies in Moyamoya disease.

In patients with MMD, specific MRI and EEG findings such as the 'ivy sign', 'brush sign', and the 'rebuilt up phenomenon' can provide

important diagnostic clues. The 'ivy sign' is characterized by diffuse leptomeningeal-sulcal enhancement visible on FLAIR and post-contrast T1-weighted images (Figure 1). The 'brush sign' refers to increased visibility of deep medullary vessels, best observed on susceptibility-weighted MRI. Another characteristic feature is the presence of tiny abnormal intracranial collateral vessels, often referred to as the 'puff of smoke', which is the most iconic sign seen on MRA images (Figure 4). The 'rebuilt up phenomenon' in EEGs describes the emergence of high-voltage slow waves following the termination of hyperventilation in children with MMD. This finding has been linked to impaired cerebral perfusion, reinforcing the consideration of MMD in patients exhibiting these EEG characteristics (28). In our series, interictal EEGs revealed hemispheric or focal slowing in five cases. While not specific to the diagnosis, this finding can serve as a warning sign, particularly in cases where hyperventilation testing cannot be performed.

The primary goal of treating MMD is to reduce the risk of ischemic attacks and hemorrhage. As per the literature, aspirin has been widely used in our series, being the preferred medical therapy for pediatric patients with asymptomatic or symptomatic ischemic type MMD or MMS (29). However, recent discussions suggest that the ischemic state in MMD is primarily due to hemodynamic rather than embolic factors, which may limit the efficacy of aspirin in preventing recurrent infarctions (6,30). Yamada et al. (31) found no significant difference in cerebral infarction rates between groups receiving and not receiving antiplatelet therapy in ischemic Moyamoya patients, with lower recurrence of infarcts observed in the surgical treatment group. Additionally, the surgical group experienced longer periods free of ischemia, and no significant variation was noted among different surgical techniques in terms of ischemia or bleeding-free intervals. Consequently, surgical interventions have gained acceptance as a more effective treatment approach. Patients who experience recurrent progressive ischemic attacks with reduced perfusion reserve are considered candidates for surgical intervention.

MMD is recognized as a progressive condition with a generally poor prognosis, particularly evident in patients under the age of four, who often experience a high incidence of cerebral infarction (32). In our study, eight patients were aged four years or younger, and six of these patients developed sequelae. This poor outcome can be attributed to the younger age distribution among these patients. Additionally, involvement of the posterior cerebral artery and recurrent episodes of bleeding are identified as additional factors contributing to a poorer prognosis in MMD.

In conclusion, MMD can manifest with both ischemic and nonischemic symptoms, necessitating a high index of suspicion for diagnosis. MRI and EEG are valuable diagnostic tools offering important clues in clinical practice.

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Original Article

The Impact of Dysnatremia on Pediatric Intensive Care Mortality

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ABSTRACT

Objective: Fragile nature of the patients in the pediatric intensive care unit (PICU) can lead to severe electrolyte imbalances with life-threatening consequences. Dysnatremia is one of the most common disorders in this setting. This study aimed to investigate the causes, severity and concomitant diseases of dysnatremia in the PICU and factors affecting mortality in these patients.

Material and Methods: This study was carried out between March 2013 and October 2014 in Ankara Children's Hematology Oncology Training and Research Hospital. The patients admitted to PICU between 1 month and 18 years of age were included in the study. Hypernatremic patients were grouped as mild (145>Na≥160 mEq/L) and severe (Na>160 mEq/L); and hyponatremic patients were also grouped as mild (120≤Na <135 mEq/L) and severe (Na<120 mEq/L).

Results: Out of the 101 dysnatremic patients (57 male/ 44 female) with a mean age of 79±71 months, 60% had hypernatremia, 40% had hyponatremia. Eighty-nine (88.1%) of the dysnatremic patients had comorbid chronic diseases, with central nervous system (CNS) disorders as the leading cause. The overall mortality rate of PICU was 17%, and the mortality rate of dysnatremic patients was 53%. The presence of concomitant chronic diseases was associated with increased mortality [OR, 3.84 (CI %95, 0.9-15.1)]. Mortality was more common in patients with severe and uncorrected hypernatremia, respectively (p=0.005, p=0.010).

Conclusion: Dysnatremia is frequent in PICU. The presence of chronic comorbidities, severe and uncorrected dysnatremia increases the risk of mortality in the PICU. Awareness of this risk is important to improve survival in these vulnerable population.

Keywords: Cerebral salt wasting, Diabetes insipidus, Hypernatremia, Hyponatremia

INTRODUCTION

Fluid and electrolyte balance is an important tool for critically ill patients and its management is vital. The fragile nature of most patients in the pediatric intensive care unit (PICU) can lead to severe electrolyte imbalances with life-threatening consequences (1). Dysnatremia is one of the most common disorders in the PICU (2, 3). Abnormal serum sodium concentrations are known to adversely affect physiological function (2, 4, 5). Cells are exposed to hypotonic or hypertonic stress due to disturbances in plasma sodium concentration (4). Therefore, dysnatremia may be associated with adverse outcomes, such as death and permanent neurological damage (2-5). The incidence of dysnatremia on admission to the intensive care unit (ICU) or later during the ICU stay varies among studies. There are publications reporting that one third of critically ill patients are dysnatremic on admission to the ICU and one third develop dysnatremia during their stay in the ICU (6, 7). These sodium disturbances can be caused by an underlying medical condition or concomitant chronic disease as well as end-organ damage, iatrogenic interventions such as fluid and electrolyte management, medications, or the use of critical care technology (8). Multicenter studies focusing specifically on dysnatremia report that it is common in the ICU and is an independent risk factor for ICU mortality (2, 7, 9). This study aimed to investigate the causes,

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

Ethics Committee Approval: This study was conducted in accordance with the Helsinki Declaration Principles. Academic approval for the study was from Ankara Pediatric Hematology Oncology Training and Research Hospital (07.05.2013, reference number: 157).

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

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severity and concomitant diseases of dysnatremia in the PICU and factors affecting mortality in these patients.

MATERIALS and METHODS

This study was designed retrospectively in PICU patients of Ankara Children's Haematology Oncology Training and Research Hospital between March 2013 and October 2014. The patients who were hospitalised with a diagnosis of hyponatraemia and hypernatraemia or who developed dysnatraemia during hospitalisation were included in the study. Patients younger than 1 month and older than 18 years of age were excluded from the study. Serum sodium levels of the patients were analysed with ion-selective method using an AU680 Beckman device. Academic approval for the study was from Ankara Pediatric Hematology Oncology Training and Research Hospital (07.05.2013-157). An informed consent was obtained from the participants and their legal guardians included in the study.

Normal sodium levels were considered to be between 135 and 145 mEq/L. Sodium values >145 mEq/L were defined as hypernatremia and sodium values <135 mEq/L were defined as hyponatremia. The classification of the etiological causes of hyponatremia and hypernatremia is shown in Table I. Severe hyponatremia was defined as a serum sodium concentration of less than 120 mEq/L while severe hypernatremia was defined as a serum sodium concentration of more than 160 mEq/L (1, 10). A blood sodium value in the range of 136-145 mEq/L as a result of the treatment given during hospitalisation in the PICU was defined as 'corrected dysnatremia' and these patients were considered as 'treatment responsive'.

Statistical Analysis

The data were analyzed using IBM SPSS Statistics for Wndows, version 21 (IBM Corp., Armonk, N.Y., USA) statistical software. Continuous data were defined as mean and standart deviation in parametric conditions and median (minimum-maximum) in non-parametric conditions. The categorical variables were defined by numbers and percentages. The nominal data were analyzed using the χ^2 test for categorical variables and Fisher's exact test for continuous variables. Logistic regression analysis was used to determine the independent risk factor for mortality. p value ≤0.050 was considered significant.

RESULTS

In this study, out of 1142 patients followed in the PICU during the study period, 101 dysnatremic patients (57 male and 44 female) with a mean age of 79±71 months were included. Sixty percent of the patients had hypernatremia and 40% had hyponatremia. Out of the 40 patients with hyponatremia, 31 had mild hyponatremia and 9 had severe hyponatremia; and out of the 61 patients with hypernatremia, 44 had mild hypernatremia and 17 had severe hypernatremia.

While 87 patients developed dysnatremia during their follow-up in ICU, 14 patients were dysnatremic at the time of admission. Respiratory failure/pneumonia (38.6%) was the most common cause of admission to PICU. Eighty-nine (88.1%) of dysnatremic patients in the study had concomitant chronic diseases. The most common concomitant disease was central nervous system (CNS) disorders such as cranial masses, cranial haemorrhage CNS infections and cerebral palsy. The characteristics of the patients are given in the table (Table II).

Table I: Etiological classification of hypernatremia and hyponatremia

Causes of Hypernatremia	Causes of Hyponatremia	
Excessive sodium intake Inappropriate concentrations of formula Consumption of sodium chloride Salt poisoning (child abuse) Iatrogenic (IV hypertonic saline/sodium chloride) Hyperaldosteronism	Pseudohyponatremia	Euvolemic hyponatremia Syndrome of Inappropriate ADH Desmopressin acetate Glucocorticoid deficiency Hypothyroidism Water poisoning Iatrogenic (excessive hypotonic iv fluid)
Water loss Diabetes insipidus Increased imperceptible losses Insufficient fluid intake	Hyperosmolality (translocational) Hyperglycemia Mannitol	Hypervolemic hyponatremia Congestive heart failure Cirrhosis Nephrotic syndrome Renal failure Capillary leakage due to sepsis Hypoalbuminemia due to gastrointestinal disease
Water and sodium losses Gastrointestinal losses Loss from skin Renal losses	Hypovolemic hyponatremia Extrarenal losses Renal losses Iatrogenic causes (diuretics) Renal diseases causing polyuria Cerebral salt loss Aldosterone deficiency (21 OH deficiency) Pseudo hypoaldosteronism type 1	

Table II: Demographic and clinical characteristics of the patients

Characteristic	Value
Gender (Male/Female)	57/44
Age (months)*	79±71 (1-210)
Hyponatremia/ Hypernatremia	40/61
Time of dysnatremia†	
During follow-up	87 (86.1)
At PICU admission	14 (13.9)
Sodium concentration (mEq/L)*	
Hyponatremia	124±5 (112-129)
Hypernatremia	157±11 (146-200)
PICU follow-up period (days)*	29 ± 35 (1-175)
PICU admission diagnosis†	
Respiratory insufficiency	39 (38.6)
Central nervous system disorders	15 (14.9)
Cardio-pulmonary arrest	12 (11.9)
Sepsis-shock	10 (9.9)
Metabolic diseases	9 (8.9)
Trauma-burn	7 (6.9)
Concomitant disease†	
Yes	89 (88.1)
No	12 (11.9)
Concomitant disease characteristic† (n=89)	
Central nervous system disorders	29 (32.6)
Metabolic	21 (23.6)
Malignity	20 (22.5)
Immune disorders	6 (6.7)
Congenital malformation/syndrome	6 (6.7)
Cardiac	6 (6.7)
Renal	1 (1.1)
Severity of hyponatremia†	
Mild hyponatremia	31 (30.6)
Severe hyponatremia	9 (8.9)
Severity of hypernatremia†	
Mild hypernatremia	44 (43.5)
Severe hypernatremia	17 (16.8)

: mean ± SD (min-max), †: n (%), **PICU: Pediatric Intensive Care Unit*

The most common cause of hypernatremia was iatrogenic diseases in 25 patients (41%). Out of these 25 patients, 10 had intravenous hypertonic fluid intake, 9 had insufficient IV hydration, 5 had diuretic use, and 1 had sodium valproate intoxication. Cerebral salt wasting in 9 patients (23%) was the most common cause of hyponatremia. The causes of cerebral salt wasting were CNS infection in 4 patients (cytomegalovirus, subacute sclerosing panencephalitis, tuberculous meningitis and bacterial meningitis), cranial metastasis in 1 patient, trauma in 2 patients and hypoxia in 2 patients. The cause of iatrogenic hyponatremia was IV hypotonic fluid administration in 3 patients, desmopressin use in 2, diuretic use in 2, insufficient IV hydration in 1. Tubular injury-related loss was found in 6 of the renal-induced hyponatremias, and oliguric state of acute kidney injury was observed in one of these patients. Of the 6 patients with extrarenal-loss caused hyponatremia, 2 had capillary leakage secondary to sepsis, 2 had gastrointestinal losses and 2 had third space losses. The causes of hyponatremia and hypernatremia are shown in Table III.

The number of patients deceased in the PICU during the study was 194, and the overall mortality rate was calculated as 17%. The mortality rate of the dysnatremic patients was 53%. This rate was

Table III: Etiology of hyponatremia and hypernatremia

Hypernatremia* (n=61)	
Iatrogenic	25 (41)
Diabetes insipidus	16 (26)
Renal (acute kidney injury)	13 (21)
Insufficient oral fluid intake	5 (8)
Extrarenal losses	2 (3)
Hyponatremia* (n=40)	
Cerebral salt wasting	9 (23)
Iatrogenic	8 (20)
Syndrome of inappropriate ADH (SIADH)	8 (20)
Renal causes	7 (18)
Extrarenal losses	56 (15)
Translocational hyponatremia (ketoacidosis)	2 (5)

**: n(%)*

50% in children with dysnatremia during admission to the PICU and 52.9% in children who developed dysnatremia during follow-up.

There was no statistically significant relationship between mortality and the development time of dysnatremia in dysnatremic patients (p=0.842). The presence of concomitant chronic diseases was associated with increased mortality [OR, 3.84 (CI %95, 0.9-15.1)] in dysnatremic patients.

In order to determine the relationship between the severity of dysnatremia and mortality; hypernatremic patients were grouped as mild (145 <Na ≤160 mEq/L) and severe (Na>160 mEq/L); and hyponatremic patients were similarly grouped as mild (120 ≤ Na <135 mEq/L) and severe (Na<120 mEq/L). Mortality was more common in patients with severe dysnatremia (p=0.005). Eighty-two (79.2%) of 101 dysnatremic patients responded to the treatment. Uncorrected dysnatremia was associated with a higher mortality (p=0.010).

DISCUSSION

In this study, most patients with dysnatremia in the PICU were observed to have concomitant chronic illnesses, and the presence of a concomitant chronic illness was associated with an increased risk of mortality in patients with dysnatremia. In addition, severe dysnatremia and uncorrected sodium disorders were found to be associated with mortality. Dysnatremia is one of the most common electrolyte imbalances in PICU. Dysnatremia may develop on admission to ICU or later during ICU stay (2, 6). The patients developing dysnatremia in the hospital was found to be more than those admitted to the hospital with a diagnosis of dysnatremia (11-15). In our study, likewise, most of the patients developed the disorder during their stay in the PICU. These results show that especially patients being followed in ICU have a risk for developing electrolyte imbalance.

Most patients with hypernatremia monitored in PICU have a related medical condition, commonly a concomitant chronic disease. Hypernatremia was also associated with higher Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) scores, a higher rate of mechanical ventilation and a greater need for inotropic/vasopressor support (14, 16). It is also stated

that patients with hyponatremia had more comorbid conditions compared to ones with normonatremia (17). In our study, almost all of the hypernatremic and hyponatremic patients had a comorbid condition or a chronic disease, in line with the literature. Unfortunately, we did not study APACHE II scores.

The most common cause of hypernatremia is iatrogenic illnesses. Iatrogenic causes are commonly inadequate IV hydration and problems reaching the liquid (6, 12). In a 21-year cohort analysis from Netherland, the incidence of hypernatremia was reported to have increased nearly 2-fold. The authors concluded that this increase was also related to such iatrogenic causes as sodium-containing infusions and drug use (18). Karlsson et al. (19) also indicate that a large proportion of documented cases of pediatric dysnatermia are iatrogenic and related to the composition of the intravenous solution (20). In our study, IV use of hypertonic fluids constitutes iatrogenic causes of hypernatremia. The frequent use of IV hypertonic saline therapy as part of the treatment of cerebral edema and frequent follow up of trauma and malignancies in PICU were thought to be the reason for this difference. Previous studies reported that syndrome of inappropriate antidiuretic hormone (SIADH) and iatrogenic causes such as IV administration of hypotonic fluid are the most comman causes of hyponatremia in hospitalized patients (2,21). In their study investigating the etiology of hospital-acquired hyponatremia, Sachdev et al. (22) reported that drug use, iatrogenic fluid intake and post-surgical processes were independent risk factors for the development of hyponatremia. In our study, cerebral salt wasting (22.5%), SIADH (20%) and iatrogenic causes (20%) were the most common causes of hyponatremia.

Dysnatremia in ICU has been shown to have an association with mortality for patients in all ages (23-25). Even daily variability in serum sodium concentration is associated with increased mortality (26). Mai et al. (24) reported that dysnatremia was associated with in-hospital mortality and poor prognosis in children with traumatic brain injury. There are several factors effecting the mortality in dysnatremic patients in PICU (24). Previous studies indicated that dysnatremia at the time of admission or during follow-up were independent risk factors for poor prognosis (2). Stelfox et al. (28) reported that acquired hyponatremia increased the risk of mortality 2-fold (27, 28). There are also studies indicating that acquired hypernatremia is correlated with increased mortality (11, 13, 29, 30). In our study, mortality was more frequent in the presence of dysnatremia. However, there was no significant correlation between the time of development of dysnatremia and mortality. This result may be associated with the small number of patients with dysnatremia at admission to the hospital in this study. Malignancies, trauma, or critical postoperative follow-ups are other important factors affecting high mortality in PICU. The relationship between mortality and dysnatremia can not be evaluated independently due to concomitant diseases occuring during follow-up (15). Dysnatremia has also been shown to cause an increased risk of mortality in the presence of organ dysfunction and concomitant chronic disease (31). Similarly, our study revealed that dysnatremic patients with chronic diseases have been associated with an increased risk of mortality.

Severe dysnatremia is associated with increased mortality. However, survival is closely related to the underlying diseases (15, 18, 32, 33). Severe dysnatremia had an increased mortality rates compared to mild dysnatremia in our study. However, most of the patients had comorbid chronic diseases, making it difficult to attribute mortality to sodium disorders alone. Uncorrected and prolonged hypernatremia is an important factor increasing the mortality (11, 34). Furthermore, the resolution of hyponatremia during hospitalization reduces the increased mortality risk conferred by hyponatremia (5, 14, 17, 35). Thongprayoon et al. (11) also reported that hypernatremia that could not be corrected within 3 days was associated with increased mortality. Similar findings have been shown in other studies (12, 15). In our study, similar to several others, sodium disorder was associated with increased mortality.

Dysnatremia is frequent in PICU. In this study, the most common cause of hypernatremia and hyponatremia was found to be iatrogenic and cerebral salt wasting, respectively. The majority of patients with dysnatremia had a concomitant chronic disease. The presence of concomitant chronic diseases is associated with increased mortality risk in the patients with dysnatremia. Moreover, severe dysnatremia and uncorrected sodium disorders are found to be associated with mortality. In conclusion, dysnatremia increases the risk of mortality in PICU. Therefore, the awareness of this risk is important for the survival of this vulnerable population.

STRENGTHS and LIMITATIONS

This study significantly contributes to the literature with the high number of patients reporting dysnatremia in PICU from a single center. This is one of the strengths of our study. The retrospective design and the unevaluated duration of dysnatremia are the limitations of our study. Another limitation of our study was that the APACHE-II scores assessing risk factors for mortality were not included.

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Original Article

Evaluation of Anterior Nutcracker Syndrome in Children: One Center Experience

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ABSTRACT

Objective: Nutcracker syndrome (NCS), caused by the compression of the left renal vein (LRV) between the superior mesenteric artery (SMA) and the abdominal aorta, is a rare clinical condition. While renal Doppler ultrasonography has been used to diagnose NCS, there have been few studies linking LRV compression measurements to symptoms in pediatric patients. This long-term retrospective study aimed to evaluate the clinical characteristics of NCS and its Doppler ultrasonographic measurements in children.

Material and Methods: Demographic, clinic, and laboratory data were collected from the medical records of patients with NCS. All renal Doppler ultrasonography (DUS) findings of the study population were also reviewed.

Results: A total of 50 patients with NCS were identified with a mean follow-up of 6.3 years. The proportion of proteinuria was 70%, and 36% of the patients exhibited symptoms of hematuria. Varicocele was also observed in 55.5% of male patients. While patients with hematuria were diagnosed earlier, patients with varicocele and proteinuria were diagnosed later in life. The mean SMA angle of patients in the supine position was significantly lower patients with varicocele (23.80±3.04° vs 27.87±4.49°, p=0.049). The estimated glomerular filtration rate (eGFR) did not differ in patients with hematuria and in patients with variocele. On the other hand, patients with proteinuria had a lower eGFR than those without (129.85±18.48 ml/min/1.73 m^2 vs 141.82±20.72 ml/min/1.73 m^2, p=0.030). The Doppler ultrasonographic parameters of the LRV did not change according to the gender, but the SMA angle decreases significantly with aging.

Conclusion: Although hematuria seems to be common, proteinuria is also common in NCS and SMA angle should thought to be important in children with varicocele.

Keywords: Doppler ultrasonography, Hematuria, Nutcracker syndrome, Proteinuria, Varicocele

INTRODUCTION

Nutcracker syndrome (NCS) is characterized by the anterior compression of the left renal vein (LRV) between the superior mesenteric artery (SMA) and the abdominal aorta (1-4). However certain variations of this condition have been described, the most common form is anterior nutcracker syndrome (2).

Nutcracker syndrome, typically presents as abdominal and/or flank pain, hematuria, proteinuria and varicocele. The prevalence of this condition is not exactly known because of the variability of symptoms at presentations and undefined diagnostic criteria (5,6).

The diagnosis is generally made by clinical presentation and also by imaging methods such as renal Doppler ultrasonography (RDUS), computed tomography (CT), magnetic resonance (MR), angiography and venography. Doppler ultrasonography is the most common used noninvasive method for the diagnosis of NCS because of its sensitivity (69–90%) and specificity (89–100%) (7-12). While RDUS has been used to diagnose NCS, there have been

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Ethics Committee Approval: This study was conducted in accordance with the Helsinki Declaration Principles. The study için was approved by the Ethics Committee of Ankara Child Health and Diseases Hematology Oncology Hospital (15.10.2018/2018-151).

Contribution of the Authors: ***YAVUZ ERAVCI S and ÇAYCI FŞ*** Conceived the study idea, ***HAKAN EDMİRKAN T*** performed Doppler ultrasonograpy, ***YAVUZ ERAVCI S and ÇAYCI FŞ*** Were responsible for literature research, ***YAVUZ ERAVCI S and KÖSE SK*** were responsible for statistical analysis, ***ÇAYCI FŞ , YAVUZ ERAVCI S*** and others took the lead in writing the manuscript. All authors discussed the results and contributed to the final manuscript.

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few studies linking LRV compression measurements to symptoms in pediatric patients (7,13-16). Therefore, we carried out a study to evaluate the clinical characteristics and its Doppler sonographic measurements in children with anterior NCS.

MATERIALS and METHODS

A study was conducted on children diagnosed with anterior NCS between January 2014 and December 2018. The study was approved by the Ethics Committee of Ankara Child Health and Diseases Hematology Oncology Hospital (15.10.2018/2018-151).

Patients with malignencies, neurological diseases, posterior NCS or other atypical variation of LRV were excluded from the study. Clinical characteristics, symptoms, positive findings on physical examination, radiologic findings, serum-urine laboratory examinations, estimated glomerular filtration rate (eGFR), body mass index (BMI) and clinical course of the patients were retrospectively analyzed.

The diagnosis of NCS was based on RDUS which showed the LRV compression in both upright and supine position in children with the presence of clinical and laboratory findings.

The cut-off value of >5.15 for the upright PV ratio (%100 sensitivity, %88.5 specificity); and >4.23 for the supine PV ratio (%69.60 sensitivity, %76.90 specificity) were used for diagnosis as stated by Fitoz et al (10). In addition, the cut-off value of <21 for the upright SMA angle (%87 sensitivity, %76.90 specificity) and <41 for the supine SMA angle were also used (10).

The presence of at least five red blood cells per high-power microscopic field in a centrifugated urine sample was classified as hematuria. Proteinuria was defined as urine protein levels greater than 4 mg/m^2/h. The eGFR (ml/min per 1.73 m^2) was calculated using the Schwartz equation. BMI was calculated as kilograms per square meter. Additionally, scrotal sonography has performed in male patients in order to evaluate the presence of varicocele.

Statistical Analysis

The data were statistically analyzed using IBM SPSS Statistics for Windows, version 11.5 (IBM Corp., Armonk, N.Y., USA) . For categorical variables, frequencies and percentages are provided as descriptive statistics, while for continuous variables, mean and standard deviation (SD) is presented. The study population was grouped based on the presence of hematuria and proteinuria, while male participants were further categorized according to the presence of varicocele. To compare two groups, the independent samples t-test was used for continuous variables with normal distribution, whereas the Mann-Whitney U test was applied for continuous variables have not normal distrubution. Categorical variables were evaluated using the Chi-square test, and correlation analysis was performed using Pearson's correlation test. A significance level of $p < 0.050$ was applied in all statistical tests.

RESULTS

A total of 50 children with anterior NCS were retrospectively analyzed. Among them 32 (64%) were female, and 18 (36%) were male. The female/male ratio was ~1.8. Age at diagnosis was 11.00 ±2.40 years for all children; 11.50±2.20 years for female patients and 10.10±2.60 years for male patients (Table I). No significant difference was found between male and female in terms of age at diagnosis (p=0.132). The most frequent symptoms were abdominal pain (48%) and dysmenorrhea (44%). Ten (55.50%) of 18 male patients had varicocele. Proteinuria was present in 35 (70%) patients and hematuria in 18 (36%). Three (6%) patients had both proteinuria and hematuria. All patients with proteinuria in the study had non-nephrotic proteinuria. The mean spot urine protein/creatinine ratio (mg/mg) of the patients at the time of diagnosis was 0.50±0.68 (0.04-3.40). Age of diagnosis was significantly higher in patients with proteinuria (11.50±1.80 vs 9.70±3.10 years, p=0.013)

Table I: The demographic features of patients with Nutcracker syndrome (n=50)

Characteristic Features	Values
Gender*	
Female	32 (64)
Male	18 (36)
Age at diagnosis (year)†	
All Patients	11.00±2.40
Female	11.50±2.20
Male	10.10±2.60
With proteinuria	11.50±1.80
Without proteinuria	9.70±3.00
With hematuria	10.10±3.10
Without hematuria	11.40±1.80
With varicocele	11.50±1.90
Without varicocele	8.30±2.50
Clinical features*	
Abdominal pain	24 (48)
Flank Pain	5 (10)
Dysmenorrhea	14 (43.8)
Varicocele	10 (55.5)

***:** *n(%),* **†:** *mean±SD*

Table II: Comparison of Doppler ultrasonographic parameters of the LRV according to the gender

Parameters	Female (n=32)	Male (n=18)	p
Supine SMA angle*	25.69±6.96°	25.37±4.21°	0.857†
Upright SMA angle*	17.59±3.47°	17.16±1.92°	0.618†
Supine PV ratio*	4.80±1.71	4.66±1.18	0.754†
Upright PV ratio*	5.81±1.64	5.49±1.26	0.480†

***:** *mean±SD,* **†:** *Independent samples t-test*

Table III: The correlation of Doppler ultrasonographic parameters with age

Parameters	Age	
	r	p*
Supine SMA angle	-0.519	0.001
Upright SMA angle	-0.380	0.006
Supin PV ratio	0.196	0.173
Upright pPV ratio	0.265	0.063

***:** *Pearson moment product correlation*

Table IV: The descriptive values for age-corrected and actual values

Parameters	Actual	Age-Corrected
Supine SMA* agle	25.57±6.04° (13.73-37.41°)	25.69±5.16° (15.58-35.80°)
Upright SMA* angle	17.43±2.97° (11.61-23.25°)	17.47±2.75° (12.08-22.86°)
Supin PV ratio*	4.75±1.52 (1.77-7.73)	4.74±1.50 (1.80-7.68)
Upright PV ratio*	5.69±1.51 (2.73-8.65)	5.68±1.46 (2.82-8.54)

**: mean±SD (95% CI)*

Table V: Comparison of adjusted Doppler utrasonographic parameters of the LRV for age according to the presence of proteinuria

Parameters	Without Proteinuria	With Proteinuria	p
Supin SMA angle*	26.84±5.86°	25.21±4.84°	0.310†
Upright SMA angle*	17.93±4.27°	17.28±1.84°	0.441†
Supin PV ratio*	4.46±0.84	4.86±1.70	0.394†
Upright PV ratio*	5.15±1.37	5.90±1.45	0.096†

**: mean±SD, †: Independent samples t-test*

Table VI: Comparison of adjusted Doppler utrasonographic parameters of the LRV for age according to the presence of hematuria

Parameters	Without Hematuria	With Hematuria	p
Supin SMA angle*	25.02±4.06°	26.90±4.70°	0.218†
Upright SMA angle*	17.33±1.84°	17.76±3.97°	0.607†
Supin PV ratio*	4.70±1.59	4.81±1.34	0.814†
Upright PV ratio*	5.71±1.56	5.61±1.30	0.811†

**: mean±SD, †: Independent samples t-test*

and with varicocele (11.50±1.90 vs 8.30±2.50 years, p=0.010). On the other hand, patients with hematuria were diagnosed in younger age (10.10±3.10 vs 11.40±1.80 years, p = 0.050) (Table I).

Serum urea and creatinine levels were found to be within normal range in all patients. The mean eGFR was 133.40±19.70 ml/min/1.73 m^2 at the end of the follow-up period. eGFR was significantly low in patients with proteinuria (129.85±18.48 ml/min/1.73 m^2 vs 141.82±20.72 ml/min/1.73 m^2, p=0.030). The eGFR did not differ in patients with hematuria (139.55±21.19 ml/min/1.73 m^2 vs 130.53±18.82 ml/min/1.73 m^2; p=0.143) and in patients with variocele (143.70 ±18.01ml/min/1.73 m^2 vs 153.25±26.79 ml/min/1.73 m^2; p=0.405). The Doppler sonographic parameters of the LRV did not change according to the gender, on the other hand the SMA angle decreases significantly with aging (Table II and III). The descriptive values for actual values and age-corrected values are given in the Table IV.

The adjusted Doppler ultrasonographic parameters of the LRV for age according to the presence of proteinuria and hematuria did not change (Table V and VI).

Doppler ultrasonographic parameters in the supine and upright positions of NCS patients with varicocele were summarized in

Table VII: Comparison of Doppler ultasonographic parameters of the LRV according to the presence of varicocele

Parameters	Without Varicocele (n=8)	With Varicocele (n=10)	p
Age at diagnosis (year)*	8.30±2.50	11.50±1.90	0.010†
Supine SMA angle*	27.87±4.49°	23.80±3.04°	0.049†
Upright SMA angle*	17.75±2.25°	16.70±1.70°	0.274†
Supine PV ratio*	5.08±1.06	4.12±1.14	0.088‡
Upright PV ratio*	5.75±1.50	5.16±0.86	0.313‡

**: mean±SD, †: Mann-Whitney U test, ‡: Independent samples t-test*

Table VII. SMA angle in the supine position was lower in patients with varicocele (23.80±3.04° vs 27.87±4.49°, p=0.049).

Five patients (10%) in the study received ACE inhibitors during the follow-up period. However, the majority of patients were treated conservatively, and none developed renal failure during the follow-up.

DISCUSSION

The frequency of NCS accompanied by clinical symptoms is not yet known. As the majority of this entrapment is asymptomatic and undiagnosed or only discovered incidentally, it is difficult to assess the exact frequency of this disease (3,17,18). Today, it is not clear why this configuration of LRV produces non-specific, variable clinical findings and why produces symptoms only in a small part of population. The three typical symptoms (hematuria, abdominal pain and flank pain) are the most clinical findings and the diagnosis of NCS may be done generally by exclusion of the other possible causes compatible with the clinical presentation in addition with imagining methods (2,3,5,19). Although venography, MRA and CTA, provide a good quality of diagnosis of this syndrome, it is very expensive and hard to perform as a first-line diagnostic tool for developing coutries and also for pediatric patients (2,7,11,12,20,21). Therefore, the RDUS measurement of the diameter of LRV, SMA angle and the peak flow velocity should be used with significant success for the diagnosis (9-12,20,21). Although most studies have been conducted with hematuric patients, the relationship of radiological compression of LRV with clinical symptoms is still unclear. In this study, 50 patients' ultrasonographic data of NCS were evaluated not only in patients with hematuria but also with other symptoms (proteinuria, varicocele).

In general opinion, NCS is more common in female patients. Although the most symptomatic patients are in their second and third decade of life, affected persons are ranging from children to older people (2). Hematuria was reported as 33.30-78.50% in children as microhematuria which was four times more common than macrohematuria (2,5,17). Although most studies have included hematuric patients, it is well known that NCS was also one of the causes of proteinuria/orthostatic proteinuria (10,22-26). Some researchers demonstrated the association of orthostatic proteinuria and NCS and suggested that NCS may be a possible cause of massive protein excretion (13,15,16). In addition, varicocele also

affects 5.50%-35.71% of men with NCS, which is related with high LRV pressure, collateral circulation leading to high resistance and pressure in the internal gonadal veins (3,17,27,28).

The pathophysiologic characteristics of NCS are not fully understood. While hematuria is due to elevated LRV pressure resulting the rupture of thin-walled veins into the collecting systems or calyceal fornix; proteinuria may due to elevated norepinephrine and angiotensin II and increased hemodynamic response and "subclinical immune injury" (2).

In our study, more than half of the patiens were female (female/male ratio ~1.8) and age of diagnosis was 11.00±2.40 years. In addition, 70% of the patients have proteinuria, %36 have hematuria and 55.50% male patients with NCS have varicocele. Most of the NCS were detected during proteinuria evaluation and the leading symptoms were abdominal and flank pain. Although the age of diagnosis was smaller in patients with hematuria, the age at diagnosis was greater in patients with proteinuria and varicocele. This can be attributed to the fact that the diagnosis of NCS is being considered in patients with hematuria rather than proteinuria and varicocele. It is well established that ruling out other causes of proteinuria requires a significantly longer time frame.

The ultrasonographic criteria for the diagnosis of NCS was reported from different studies as the ratio of the AP diameter >4.20 and as the ratio of PV 4.00-5.00 (3,7,13). On the other hand, Fitoz et al. (10) reported the cut-off value of >5.15 for the upright PV ratio as 100% sensitivity and 88.50% specificity. In addition, the cut-off value of <21 for the upright SMA angle (87% sensitivity, 76.90% specificity) and <41 for the supine SMA angle were also reported (10). However, as we mentioned above, association of RDUS measurements of the LRV with clinical symptoms are still remains unknown.

While no significant differences was reported in children for the PV at the hilar portion between the NCS and normal children, significantly lower PV at the hilar portion was also reported in adults with hematuria (6,11). Again, the degree of compression of the LRV with abdominal pain, hematuria, and proteinuria was also reported as significantly high in NCS (diagnosed with CT) compared with controls (29). As seen, all these studies were generally conducted by comparing NCS with healthy control groups.

In our study, patients were compared according to the presence or absence of proteinuria and hematuria for age, and Doppler ultrasonographic parameters of the LRV did not change. In addition, we have found the mean SMA angle of our patients in the supine position was significantly lower in patients with varicocele.

However, we have also some limitation; first, we have small number of patients with NCS; second, MR imaging, CT, or venography were not used as a reference standard to confirm the diagnosis of NCS.

CONCLUSION

In conclusion, to our knowledge there are few studies in children which compares the RDUS radiological measurements of LRV and the clinical symptoms with NCS. By reporting this study, we would like to emphasize the importance the SMA angle measurement on clinico-radiological correlation. Although hematuria seems to be common, proteinuria is also a common finding and patients with proteinuria and varicocele should also be evatuated for NCS.

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