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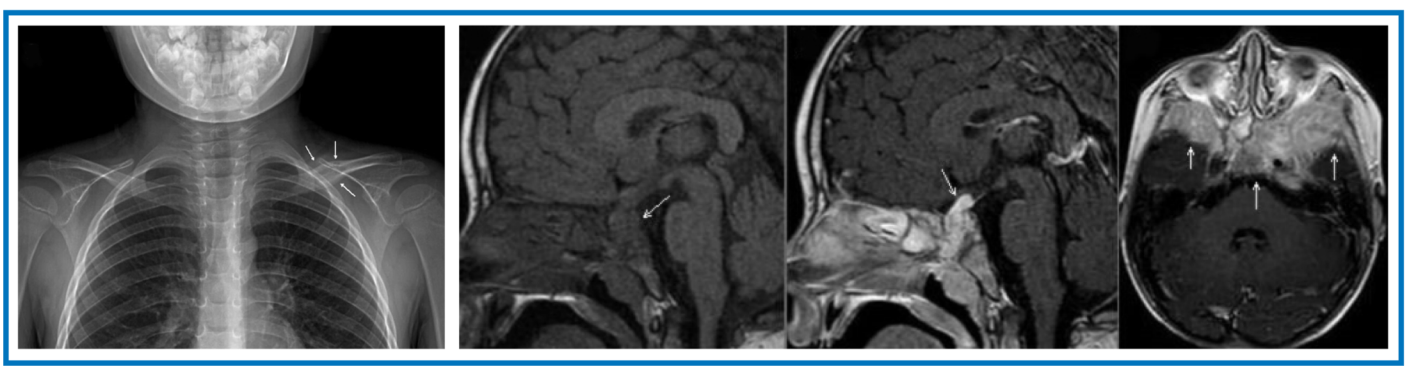

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Contents

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Editorial

Dear Trends in Pediatrics readers,

We are happy to present the second issue of this year which includes four original articles, three case reports, and a comprehensive review of multisystem inflammatory syndrome in children (MIS-C) which is a rare but severe complication of SARS-CoV-2 infection.

I would like to thank all of authors and reviewers who have contributed to the success of our journal.

I would like to express my deepest respect to all healthcare professionals who lost their lives due to the SARS-CoV-2 pandemic.

Sincerely yours,

Ahmet Anık
Editor-in-chief

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Review

A Novel and Severe Clinical Picture Related to COVID-19: Multi-Inflammatory Syndrome in Children

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ABSTRACT

Preliminary data have suggested that children have milder COVID-19 disease course compared to adults. However, pediatric cases with severe clinical findings caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) are being reported since April 2020. These children have been presented with significant hyperinflammatory states resembling Kawasaki disease, toxic shock syndrome, and macrophage activation syndrome. However, they had several distinct features, as well. Therefore, this novel condition was considered a unique disease and named Multi-inflammatory syndrome in children (MIS-C). Thus, new concerns have been raised regarding the vulnerability of the children. However, it has been realized that this condition is extremely rare. Nonetheless, considering that it is a life-threatening disease and may cause devastating consequences, clinicians should be aware of MIS-C while evaluating children with persistent fever and history of COVID-19 contact or active infection.

INTRODUCTION

In December 2019, a cluster of pneumonia cases with atypical and severe symptoms emerged in Wuhan Province of China. Due to the distinct clinical features of these patients, advanced laboratory investigations were performed, and a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was isolated for the first time. The disease caused by the virus was also novel and named coronavirus disease 2019 (COVID-19). Then, the virus spread worldwide, and due to the rapidly increasing number of patients, World Health Organization declared this outbreak as a global pandemic on March 11, 2020.[1]

The clinical findings of COVID-19 range in a large scale between an asymptomatic carriage and severe presentations such as acute respiratory syndrome (ARDS) and multiorgan dysfunction.[2,3] Fortunately, early data revealed that children have a milder disease course and better prognosis compared to adults.[4,5] Thus, the idea of the children is almost not affected by the pandemic was prevalent. Families did not sufficiently insist on their children wearing a mask or keeping the social distance, and several

governments loosened the school attendance restrictions.

However, this positive discrimination in favor of children provided by the virus did not last so long. In April 2020, SARS-CoV-2 was isolated from eight children with suggestive symptoms of Kawasaki disease (KD), such as fever, conjunctivitis, and peripheral edema. In addition to KD- resembling features, those children had gastrointestinal symptoms such as vomiting and diarrhea and developed refractory shock.[6] Subsequently, it has been shown that SARS-CoV-2 may also induce a hyperinflammatory state in children resembling toxic shock syndrome (TSS) and macrophage activation syndrome (MAS) rather than KD.[7,8] Therefore, the Centers for Disease Control and Prevention (CDC) recognized this SARS-CoV-2-induced hyperinflammatory condition as a novel disease and named it as multisystem inflammatory syndrome in children (MIS-C).[9]

Recent findings regarding MIS-C suggest that children are not thought to have host advantages against SARS-CoV-2 as much as previously considered. Therefore, in this review article, we aimed to contribute to a better understanding of this novel disease.

Epidemiology

A male dominance among the patients was shown in several studies.[10-12] A systematic review evaluating 917 MIS-C patients showed that the median age of the patients was 9.3 years, and 56.8% of the cases were males.[13] Similarly, male/female ratio was 1.37:1, and the median age was 7.5 years in another systematic review including 992 MIS-C patients.[14] It is well known that the current pandemic was originated from East Asia. Besides, KD is in the differential diagnosis of MIS-C mostly seen in Asian children.[15] On the contrary, there is an Afro-Caribbean and Hispanic ethnic predominance among the MIS-C patients.[16] These intriguing findings make us consider that a genetic predisposition or environmental circumstances may play a pivotal role in the pathogenesis of MIS-C.

Pathogenesis

Although it has not been precisely elucidated yet, there are several suggested mechanisms for explaining the pathogenesis of MIS-C. Children diagnosed as MIS-C usually have contracted SARS-CoV-2 infection two to four weeks before the onset of MIS-C symptoms.[17] There is an overall four-week interval between the date of the peak incidence of the outbreak and the date of the observation of MIS-C patients for the first time.[18-21] Besides, it has been demonstrated in several studies that positive antibody testing is much more common than polymerase-chain reaction (PCR) test positivity among MIS-C patients.[22-24] These findings strongly suggest that a post-infectious process rather than a direct viral invasion is responsible for the pathogenesis of the disease.

There are also conflicting hypotheses. For instance, a decreased SARS-CoV-2 antibody activity in patients with MIS-C compared to COVID-19 patients has been recently shown. Therefore, a persistent infection was speculated to be the main pathogenic mechanism instead of a post-infectious syndrome.[25] Consistently, Colmenero et al.[26] demonstrated viroid particles of SARS-CoV-2 in the skin biopsies of seven children who presented with chilblain four weeks after the peak incidence of the outbreak in their geographical region, similar to the MIS-C patients.

Since there are several clinical similarities between TSS and MIS-C, studies focused on investigating the molecular proof of this similarity have been also performed.[27] It is already known that staphylococcal enterotoxin B (SEB) has a superantigen (SAg) motif, and this motif causes host-cell damage via inducing a massive release of inflammatory cytokines.[28] Similar to SEB, SARS-CoV-2 has also been shown to encode a protein that shares remarkable sequential and structural similarities with SAgs.[29,30]

A study evaluating 58 MIS-C patients reported that while the PCR test was negative in most of their patients, SARS-CoV-2 antibody test results were positive. Besides, majority of them had significantly elevated inflammatory markers, and anakinra (anti-IL-1 agent) and achieved a prominent clinical improvement. Therefore, they suggested that the possible mechanism of action of the disease is an exacerbated post-infectious hyperinflammatory response.[31]

Similarly, most of the patients presented with cardiac signs and increased inflammatory markers, and as reported by Kaushik et al.[32] they had antibody positivity against SARS-CoV-2. Given that there is no strong evidence for the cardiac tropism of the virus, they proposed that an antibody-induced cytokine storm may be responsible for the tissue damage.

Clinical features

The first cases with SARS-CoV-2- induced hyperinflammation were reported by Riphagen et al.[6] from the United Kingdom (UK). As it was mentioned before, the patients all had KD- like symptoms such as fever, conjunctivitis, peripheral edema, and extremity pain. Moreover, they had gastrointestinal features such as diarrhea, vomiting, and abdominal pain. However, none of them had significant respiratory involvement. One of the patients who developed cardiac dysrhythmia and received extracorporeal membrane oxygenation (ECMO) therapy unfortunately died. An unclear linkage between KD and SARS-CoV-2 was emerged.

Following this study from the UK , Chiotos et al.[33] described six patients with MIS-C. Similarly, they had KD-like features, gastrointestinal symptoms, and shock. Among ten MIS-C patients reported from Italy, in addition to KD-like symptoms such as fever, rashes, conjunctivitis, mucositis, and lymphadenopathy, the patients had diarrhea (n:6), hypotension (n:5), pneumonia (n:5), and meningeal signs (n:4).[22]

However, subsequently reported cases with SARS-CoV-2- induced hyperinflammation had distinct aspects from the KD. Rather than the KD, given the clinical and laboratory similarities such as fever, refractory shock, organ damage signs, and complete blood count, cytokine, inflammatory markers, and lipid profiles, TSS and MAS were also emphasized in the differential diagnosis of MIS-C, as well.[17,34,35]

In the study which reported the first MIS-C cases from New York City, although all the patients were seropositive, only seven of fifteen cases had a positive PCR result. While all the patients had fever, the patients also had severe cardiac involvement (n:13), gastrointestinal features (n:13), skin changes (n:7), respiratory involvement (n:7), conjunctivitis (n:4), peripheral edema (n:4), and 9 cases required treatment with inotropic or vasopressor agents. Levels of acute phase reactants increased in most of them, whereas platelets, lymphocytes, and serum albumin levels decreased.[36]

It was shown in a retrospective study that following the fever, the most common symptoms among MIS-C patients were gastrointestinal involvement, conjunctivitis, erythematous rash, and oral changes.[37] A study from Turkey, including 36 MIS-C patients, reported that the most common symptoms were fever, mucocutaneous rashes, and gastrointestinal symptoms, respectively.[38] Fever and abdominal pain were the most common symptoms in a study of Tolunay et al.[39] The first report regarding the MIS-C from East Mediterranean Region compared COVID-19 and MIS-C and revealed that the patients with MIS-C had a higher duration of fever and higher rates of rashes and conjunctivitis.[40]

According to a systematic review article, the most common clinical findings out of fever were as follows: gastrointestinal (87%), muco-cutaneous (73%), cardiovascular (71%), respiratory (47%), neurological (22%), and musculoskeletal (21%) symptoms.[16] Similarly, it has been revealed in a more current systematic review that the two most common symptoms of MIS-C patients were fever and gastrointestinal symptoms.[16]

It was previously mentioned that MIS-C mainly occurs in school-age children and adolescents. However, there is a recent paper describing ten infants with MIS-C. Unlike seen in older ones, the most common finding other than fever was rashes. Five patients had respiratory distress, and one had febrile convulsion. Unfortunately, two with congenital heart diseases died.[41]

Considering the underlying pathogenic mechanism of MIS-C, in addition to TSS, MAS, and KD- like symptoms, a variety of organ damage or inflammation signs are already expected. For instance, several MIS-C patients initially presented with acute abdomen- like signs such as acute appendicitis.[42,43] Furthermore, it is well known that MIS-C patients may have severe cardiac compromise at high rates that can be considered life-threatening events.[44]

Therefore, to prevent unnecessary surgical operations during the pandemic, it has been suggested that pediatric surgeons perform a myocardial evaluation and rule out the MIS-C in children who presented with acute abdomen.[45]

Although any segment of the gastrointestinal tract can be compromised, there is a predominance of ileal and colonic inflammation among the patients. Progressive bowel obstruction which mainly recovers with medical treatment may occur. However, a minority of the cases may require surgical resections.[46]

In a retrospective study, acute kidney injury (AKI) was seen in ten of fifty-five MIS-C patients. AKI developed at admission in most of them which were associated with lower serum albumin levels and higher white blood cell counts.[47]

Two out of 9 MIS-C patients recently reported from Germany had unusual findings. One developed encephalomyelitis. The other had been newly diagnosed with acute leukemia, just a few weeks after the onset of SARS-CoV-2 infection. Two days after the chemotherapy, this male patient had a sudden respiratory failure and was diagnosed as MIS-C in the intensive care unit. However, it remains unclear whether chemotherapy or the virus triggered leukemia.[48]

Thirty-five patients admitted to the pediatric intensive care unit due to acute heart failure and hyperinflammatory condition were evaluated in a multicenter study, and SARS-CoV-2 infection was proven in thirty-one of them.[49] Furthermore, Stevens et al.[50] reported a MIS-C patient who initially presented with acute pancreatitis, and Kashyap et al.[51] reported a seven-month-old patient with MIS-C-related status epilepticus.

We also encountered children with MIS-C in our daily practice. There was a slight male predominance, and cases were mostly school-age children and adolescents, similar to the current literature.[13,14] While the PCR tests were negative in most of them, they were seropositive against SARS-CoV-2. Fever and gastrointestinal symptoms were the most common symptoms. Although not pointed out before, rashes of our patients were mostly well-demarcated and round shaped. We presented rashes of some of our patients below (Figure 1). Thrombocytopenia, lymphopenia, abnormal cardiac enzymes, and elevated acute phase reactants were the most common laboratory findings. Overall, one third of the patients required intensive care due to respiratory failure or other severe organ damages. All but one recovered completely. Unfortunately, one patient who previously received the diagnosis of acute lymphoblastic leukemia died.

Diagnosis

Considering the similarities and differences between the hyperinflammatory conditions caused by SARS-CoV-2, and KD, TSS, and MAS, this novel entity was considered to be a unique disease by CDC, and its diagnostic criteria were established (Table 1).[9,52]

Table 1. Diagnostic criteria of MIS-C

Case Definition for MIS-C (48)

- An individual aged <21 years presenting with fevera, laboratory evidence of inflammationb, and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological); **AND**
- No alternative plausible diagnoses; **AND**
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test or COVID-19 exposure within the four weeks before the onset of symptoms.

COVID-19, coronavirus disease 2019; IL, interleukin; MIS-C, multisystem inflammatory syndrome in children; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a] *Fever ≥38.0°C for ≥24 hours or report of subjective fever lasting ≥24 hours.*

[b] *Including, but not limited to, one or more of the following: an elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase, or IL-6; elevated neutrophils; reduced lymphocytes; and low albumin.*

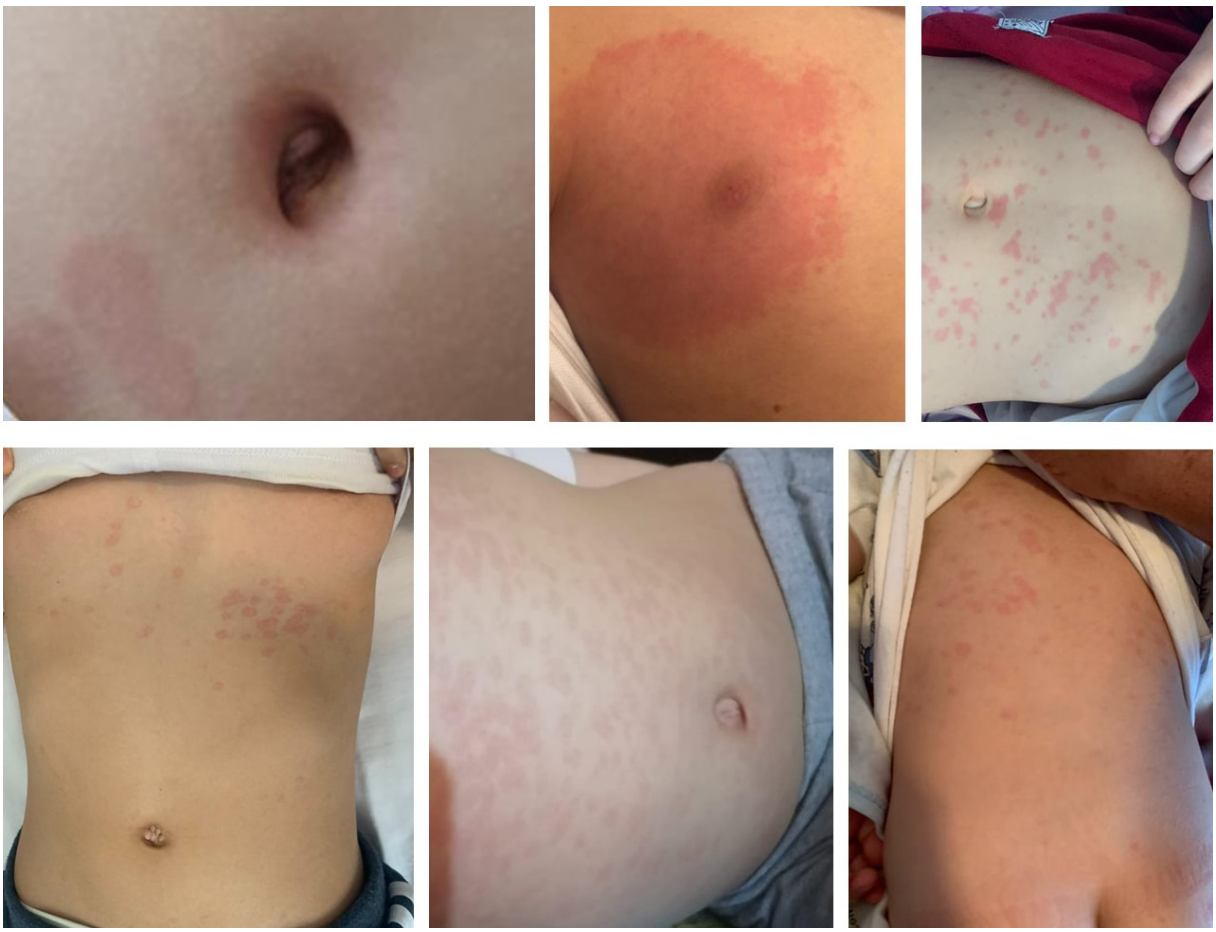

Figure 1. The rashes seen in some of our MIS-C patients

Treatment

Since highly suggestive symptoms for KD are seen in patients with MIS-C, early cases were treated with intravenous immunoglobulin (IVIG) and acetylsalicylic acid similar to the patients with KD, and favorable outcomes have been achieved.[6,49,53] Moreover, immunomodulatory treatment options such as anakinra and tocilizumab were given to IVIG and steroid non-responders which were found to be highly effective.[31,32,53]

Given that the MIS-C is a hyperinflammatory condition, steroids were widely used based on their well-known strong anti-inflammatory effects although their safety and efficacy remain unclear.[17] In a study from Istanbul, seven of twenty MIS-C patients required intensive care. While IVIG responses of the patients were inadequate, steroids were observed to have a dramatic effect.[54]

In our daily practice, all patients with MIS-C are initially given IVIG at a dose of 2 gr/kg as the first-line treatment. If there is shock or organ threatening event, methylprednisolone (1-2 mg/kg/day) is added. To the refractory cases, methylprednisolone (10-30 mg/kg/day) or high dose anakinra is given as the second-line treatment. Moreover, all of the MIS-C patients receive acetylsalicylic acid unless active bleeding or platelet count is lower than 80 000/ mm^3.[55] Plasmapheresis is performed in patients with resistance to medical treatment options in our center, and most of our refractory cases clinically have improved so far. We tried to summarize schematically our therapeutic approach (Figure 2).

In a study from the United States, infliximab (an anti-tumor necrosis factor-alpha agent) was given to 12 of 13 IVIG and steroid non-responder MIS-C patients, and all of them recovered.[56] Consistently, as recently

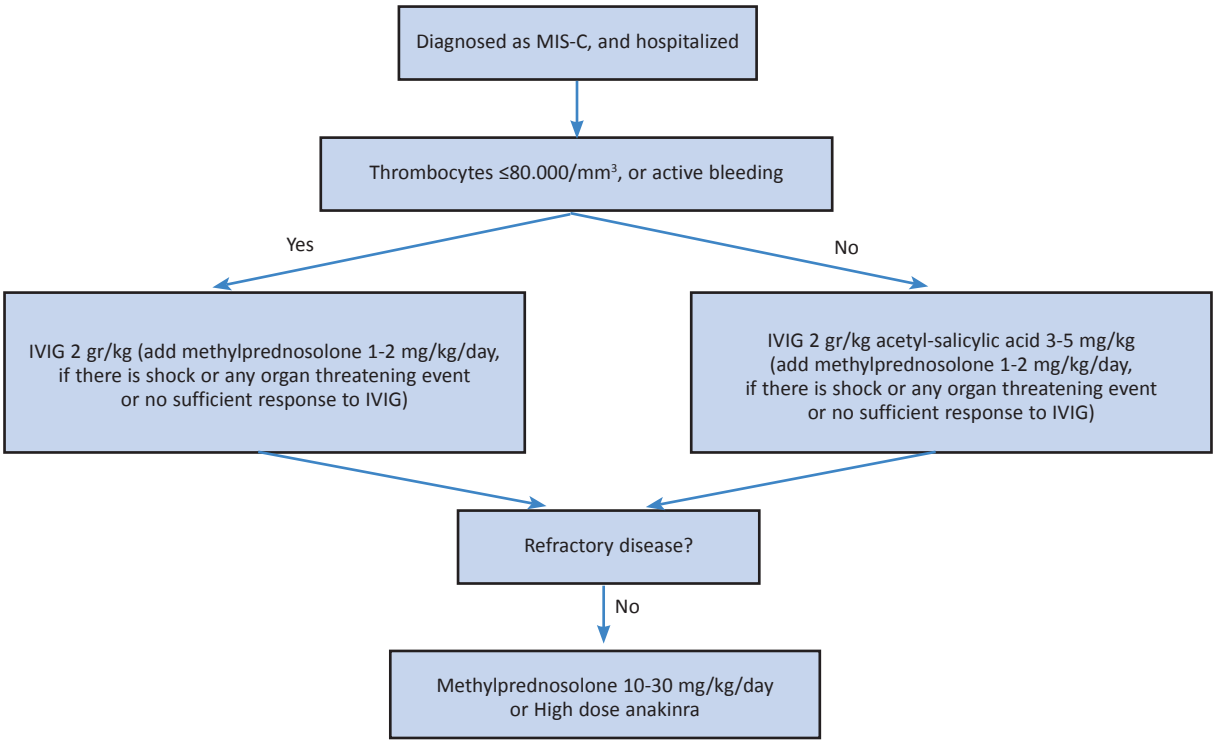

Figure 2. Our therapeutic approach for the MIS-C

reported by Alkan et al.[57] the authors had given infliximab to a MIS-C patient with underlying inflammatory bowel disease, and they achieved clinical recovery.

Although there is insufficient data regarding the safety and effectiveness of highly invasive procedures such as ECMO, they may be performed in medically intractable MIS-C patients.[58]

CONCLUSION

In conclusion, MIS-C is a less understood, rare, and highly fatal complication of COVID-19. Given the recent data regarding MIS-C, children are not thought to be in a favorable position during the pandemic as was presumed previously. Clinicians should be aware of this novel disease while evaluating children with persistent fever and history of COVID-19 contact or active infection. Since the clinical signs may rapidly deteriorate in these patients, medical treatment should be promptly started if there is a diagnostic suspicion. Besides, it has been recently seen that these patients could present with many distinct clinical pictures such as acute appendicitis or pancreatitis. Therefore, particularly in these extraordinary days, MIS-C should always be kept in mind for children with unusual signs and symptoms.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Original Article

The Effect of The Height of a Second-Degree Relative on Children with Short Stature

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ABSTRACT

Objective: *This study aimed to investigate the effect of the heights of second-degree relatives on adult height.*
Methods: *This was a cross-sectional study. Healthy children who applied to the general pediatric outpatient clinic to monitor the development of growth were considered as control group. Case group consisted of patients over 3 years of age with genetic, idiopathic short stature or without short stature but below the target height. All participants had either an uncle and an aunt with a short stature. Two groups were compared for their demographic characteristics and family information.*
Results: *The control group consisted of 43 children who were older than 3 years. A total of 101 cases of short stature were included in the study. Prevalence rates of idiopathic (39.6%: n=40), familial (36.6%: n=37), and constitutional (23.7%: n=24) short stature were as indicated. When the males included in the study were examined from different perspectives (case, control, presence of consanguineous marriage), the height of the uncle was predicted to be closer to or equal to the target height.*
Conclusion: *In case of short stature, the 'target height' criterion alone is shown to be not reliable in the assessment of genetic compatibility as well as the deviation from the predicted final height. Predicted final height was demonstrated to be similar to aunt height for girls and uncle height for boys. Therefore, the height of a second-degree relative can be used as an aid in the estimation.*

INTRODUCTION

Short stature (SS) is defined as having the height below the 3rd percentile according to age and sex, or having two standard deviations lower than the average by age and sex. SS, affecting 2%-3% of the population, is a serious problem that is one of the main reasons for applications to pediatric endocrinology outpatient clinics.[1] Since height is one of the most important indicators of growth in children, differential diagnosis of SS is possible by primarily evaluating growth. However, not all children below the 3rd percentile show a pathology for growth, most of them are healthy children called variants of normal.[2] Approximately 2/3 of the applications to the reference endocrine centers with the complaint of SS in the evaluation of growth consist of children with variants of normal.[2] Familial (genetic) SS (FSS) is a definition used for children whose current height is below the 3rd percentile, but whose height is suitable for their target height (TH).[3] Although the child with constitutional SS, has a normal height at birth and in the first year of life, her/his height measurements gradually fall below the 3rd percentile.[4] In the literature, there is no significant difference in the proportion of SS between

boys and girls in terms of numerical distribution for age groups. In many studies conducted around the world and in our country, variant SS is the most common cause.[5,6] Since the most common cause is variant of normal, including FSS, the role of genetic factors has to be examined carefully. Human height is a complex feature under the control of both genetic and environmental factors. The inheritance rate of the height is above 50% and the inheritability of the height is the highest among complex human characteristics.[6,7] In addition to genetic factors, many factors such as intrauterine conditions, the environment in which the child is raised, nutrition, endocrine factors, diseases, socioeconomic status and psychological state affect final height.[3] Genetic effects in linear growth are associated with more than one gene. There is a 50% similarity between mother, father and siblings and the genes of the child, 25% with grandmother, grandfather, uncle-aunt and 12.5% with cousins.[8] If the individuals with SS in the family are closer to the child in terms of consanguinity, then the child will more likely have an SS.[2] Although the genetic effect of parental height on the child's height is known, and anthropometry of relatives are considered to be important for short stature cases; there is no study in the literature on the possible effect of the height of second-degree relative on final height.[9] To the best of our knowledge this study firstly aimed to investigate the possible effect of second-degree relatives on final height in the literature.

Methods This was a cross-sectional study completed within one year. Ethics committee approval was received from study hospital's local ethics committee for this study. Informed consent was obtained from parents and children. The case group consisted of the patients who were followed up in the outpatient clinic of Pediatric Endocrinology and Nutrition-Metabolism of our hospital. Children, who were followed up for routine care of healthy child at pediatric outpatient clinic of study center, consisted the control group. The case group consisted of patients with familial SS, idiopathic SS, without SS but remained below the target height (TH), and also had aunt(s) and uncle(s). SS was defined as having the height below the 3rd percentile according to age and sex, or having two standard deviations lower than the average by age and sex using reference values for Turkish children.[10] Familial SS is used for children whose current height is below the 3rd percentile, but whose height is suitable for their TH.[3] The term idiopathic short stature (ISS) is used for those whose height is above 2 standard deviations but below the median height for gender and age without systemic, endocrine and/or chromosomal abnormalities.[11] Pathologic short stature, being under the age of three years old, inadequate information, history of growth supplementation and lack of consent were reasons for exclusion. The children who did not have either a paternal aunt and a maternal uncle were also excluded. The heights of maternal uncle and paternal aunt of all participants were presented. In case of multiple aunts and/or uncles, the one who had the lowest height was included. Demographic characteristics of all patients were obtained. Age, sex, weight (kg), height (cm), target height (cm), predicted final height (PAH), bone age, puberty staging, maternal height (MH), paternal height (PaH), heights of the aunt (AH), and the uncle (UH), age of the mother were recorded. The presence of parental consanguinity was noted. The heights of the individuals were measured while standing on barefoof, by the same trained person using a Harpenden Stadiometer sensitive to 0,1 cm.

Weight measurements were performed by the same trained person using a portable scale sensitive to 0.1 kg.

Bone age was determined by the same physician with the help of the hand - wrist atlas developed by Greulich - Pyle on the left-hand wrist radiograph. The Bayley - Pinneau method was used to calculate the PAH. According to Tanner's TH formula, TH is calculated as (mother's height + father's height) /2±6.5 cm.

Statistical Analysis

Mean, standard deviation (SD), ratio and frequency values were used in descriptive statistics of the data. A sample size of 144 infants, at least 43 in each arm, is found to be sufficient to detect a clinically important difference between groups with 80% statistical power and a 5% level of significance. The data distribution was analyzed by Kolmogorov -Smirnov test. Independent sample t- test and Mann-Whitney U test were used for the analysis of the quantitative data. Chi-square test was used in the analysis of qualitative data. All data were shown as mean ± SD.

p <0.05 was considered significant. Statistical analysis was performed using SPSS 20.0 for Windows.

RESULTS

The study included 101 cases and 43 healthy children who were followed up in the outpatient clinic of Pediatric Endocrinology and Nutrition - Metabolism at study hospital. Demographic features of the study population are demonstrated in Table 1. There was no statistically significant difference between case and control groups as for distribution of genders, age, patients' height, and weight, bone age, AH, UH, puberty ratio and patient characteristics (Table 1). PAH in the case group was significantly lower in the control group (Table 1). In the case group, TH, MH, PaH and maternal menstruation age were significantly higher than the control group (all p <0.05) (Table 1). TH was significantly higher than the PAH in the case group (Table 2). Girls' TH and AH values were similar and both characteristics were significantly higher than the PAH in the case group (Table 2). No significant difference was found between girls' PAH vs TH and PAH vs AH (Table 2). TH and UH of boys were similar and both characteristics were not significantly different from the PAH in the case group (Table 2). In the control group, TH and AH of girls were similar and both of these parameters had no significant difference from the PAH (Table 2). In the control group, TH and UH of boys were significantly shorter than PAH (Table 2). The difference between PAH - TH was significantly higher than the difference between PAH, and UH in the boys of the case group (Table 2). In the case group, TH and AH values were significantly higher than PAH of girls who did not have a history of parental consanguinity (Table 3). UH and TH were similar in boys without a history of parental consanguinity and those measures did not differ significantly from PAH in the case group (Table 3). In the control group, TH and AH values were not different than PAH of girls without a history of consanguineous marriages (Table 3). In the control group, TH and UH were significantly lower than PAH of boys without a history of parental consanguinity (Table 3). Besides, the difference between PAH, and TH was significantly higher than the difference between PAH, and UH in boys without a history of parental consanguinity (Table 3). In the case group with a history of parental consanguinity. TH and AH of girls were significantly higher than their PAHs

Table 1. Comparison of demographic data between groups

	Case Group (n=101) n (%) Mean±SD/SDS	Control Group (n=43) n (%) Mean±SD/SDS	p
Gender			
Female	48 (47.5)	19 (44.2)	0.713
Male	53 (52.5)	24 (55.8)	
Age	10.06±3.77	9.60±3.45	0.498
Predicted Height (cm)	159.79±12.70	166.72±11.70	**0.007**
Target Height-SDS (cm)	2.80±0.8	2.92±0.43	0.749
	163.51±9.35	160.09±7.86	0.117
Height-SDS (cm)	-2.83±1.07	2.54±0.35	**<0.001**
	(124.88±19.13)	(131.40±21.60)	0.074
BMI-SDS	0.76±0.44	0.63±0.34	0.669
	(14.83±2.59)	(14.31±2.22)	0.072
Bone Age	8.71±3.91	9.21±3.88	0.486
Maternal Height	156.7±6.7	153.6±5.3	**0.007**
Paternal Height	169.9±7.1	165.2±8.5	**0.001**
Aunt Height	157.8±8.3	156.1±6.9	0.263
Uncle Height	170.2±6.5	170.7±6.4	0.650
Puberty			
No	58.0 (57.4)		0.858
Yes	43.0 (42.6)		

Chi-Square/Independent sample t test
Abbreviations: BMI: body mass index, SD: Standart deviation, SDS: standart deviation score

Table 2. Comparison of predicted height, target height and second degree relatives' heights between groups

		Difference from Predicted Height			
		Mean±SD	**p**	**Mean±SD**	**p**
Case Group	Female Predicted Height Target Height Aunt Height	150.1±7.3 156±5.5 156±7.4	**<0.001** **0.001**	5.9±8 6±9.9	0.995
	Male Predicted Height Target Height Aunt Height	169.4±9.1 169.7±5.6 170.9±6.2	0.821 0.312	0.3±7.8 1.7±9.1	0.117
Control Group	Female Predicted Height Target Height Aunt Height	157.2±7 154.7±5.5 154.5±6	0.056 0.15	2.5±5 2.7±7.4	0.879
	Male Predicted Height Target Height Aunt Height	175.2±7.8 165.4±5.9 171.1±4.4	**<0.001** **0.043**	9.8±6.9 4.2±8.2	**0.001**

Paired sample t test

Table 3. Comparison of predicted height, target height and second degree relatives' heights between groups without consanguineous marriage

		Difference from Predicted Height			
		Mean±SD	**p**	**Mean±SD**	**p**
Case Group	Female Predicted Height (cm) Target Height Aunt Height	149.9±6.0 155±5 155.7±7	**0.002** **0.011**	5.1±8.1 5.8±11.1	0.643
	Male Predicted Height Target Height Aunt Height	169.2±9.4 169.9±6 171.2±6.8	0.642 0.297	0.6±7.5 2±9.7	0.203
Control Group	Female Predicted Height Target Height Aunt Height	158.2±7.2 155.4±5.8 155±5.9	0.067 0.113	2.7±5.2 3.2±7.1	0.778
	Male Predicted Height Target Height Aunt Height	176.7±6.5 166.5±6.1 171.8±4	**<0.001** **0.002**	10.2±6.1 5±4.9	**0.003**

Paired sample t test

(Table 4). Also, the difference between PAH, and AH was lower than the difference between PAH, and TH of girls (Table 4). TH and UH of boys did not differ significantly from PAH in the case group with a history of parental consanguinity (Table 4). In the control group with a history of parental consanguinity, TH and AH of girls were not significantly different from PAH (Table 4). TH and UH of boys did not differ significantly from PAH in the control group with a history of parental consanguinity (Table 4).

Table 4. Comparison of predicted height, target height and second degree relatives' heights between groups with consanguineous marriage

		Difference from Predicted Height			
		Mean±SD	p	Mean±SD	p
Case Group	Female				
	Predicted Height (cm)	150.7±10.5			
	Target Height	158.8±6.4	**0.008**	8.2±7.5	0.527
	Aunt Height	157±8.7	**0.008**	6.4±5.9	
	Male				
	Predicted Height	170.1±8.5			
	Target Height	169.3±4.5	0.773	0.6±9	0.327
	Aunt Height	170.3±4.5	0.927	0.7±7.1	
Control Group	Female				
	Predicted Height	152.7±4.7			
	Target Height	151.3±0.6	0.686	1.3±5	0.826
	Aunt Height	152.3±7.5	0.959	0.3±9.9	
	Male				
	Predicted Height	171±10.3			
	Target Height	162.4±4.8	0.124	8.7±9.7	0.123
	Aunt Height	169.2±5.5	0.797	1.9±14.6	

Paired sample t test

DISCUSSION

Although SS is a health problem affecting 2%-3% of the population, there is no significant difference in the prevalence rate of SS between boys and girls in terms of numerical distribution for age groups.[9] The idea that there may be more criteria than TH calculation is required in the assessment of height and PAH estimation formed the starting point of our study. In a study conducted in 2009, the control of compliance of human height with the genetic potential introduced a stimulating criterion, especially in cases with slight deviation of stature in growth chart, and predicted that the reliability of TH was not the same in all cases.[12] In this study, it has been proven that as the degree of deviation in height increases, the incompatibility of height to genetic potential becomes evident. Therefore, the confidence interval of TH decreases, especially in case of SS and this finding necessitates new evaluation methods other than using this criterion.[12] Distributions of SS in pediatric endocrine outpatient clinics do not match the rates given for the normal population. In the interpretation of short stature in children, adaptation to the genetic potential should not be neglected in addition to height deviation. Not all idiopathic short stature cases show normal variant characteristics. This perspective is important for further investigation and treatment approaches. The most frequent type of SS is determined as constitutional SS in boys and familial SS in girls.[13] Overall, Lindsay et al.[14] reported pathological causes accounted for 18.9% and Bhadada et al.[7] 63.9%, Zafer et al.[15] 34.3%; Topal et al.[16] 47.1% of cases with SS. Variability in these findings may be due to differences in socioeconomic conditions. As the socioeconomic level increases, the frequency of admission to patients with variant SS increases and pathological causes can be caught earlier and treated without the development of severe SS.[17] In many studies conducted around the world and in our country, variants of normal is the most common cause.[6,15] In this study, the most common reason for SS was the variance of normal SS with a rate of 60.3%. In the variant of normal, SS does not show a significant difference from the final height. Since the variant of the normal was the cause of the majority of the individuals included in our study, this was a factor that decreases the statistical significance of the results. For stronger statistical results, new studies may be required in which long-term evaluation of cases is performed. While it is stated that familial SS is in the foreground in girls, constitutional SS is the mostly seen one in boys.[15]

In the present study, familial SS in boys was the leading cause with a rate of 40.4% (n=21). It was seen that idiopathic SS was the most common cause in girls with a rate of 46.9% (n=23). This may be due to the fact that the SS distribution in patients referred to the pediatric endocrine outpatient clinic, varies with the normal population. According to the subject of the study, it is expected that the presence of consanguineous marriage will significantly increase the similarity between the heights of second-degree relatives. The rate of consanguineous marriages in our study was 25% (27% in the case group, and 20% in the control group) and was similar to the 20% (17% in Istanbul and Izmir - 36% in the villages) reported in the literature for Turkey.[18] When the groups with and without consanguineous marriages were compared without gender discrimination, no significant difference was found (data not shown). However, when only male gender was considered, it was concluded that UH was closer to PAH than TH in both case and control groups. In girls, there was no significant difference between the groups with and without a history of consanguineous marriages. This can be explained by the fact that the maternal height is very similar with UH in families with consanguineous marriages and that the height of girls is less inheritable than boys. When only the case group is considered, although AH has no superiority to TH, AH can be used instead of TH for girls. In this study, the most common cause of idiopathic factors in girls may have contributed to this result. In a study conducted in 2011, SS was found in index cases and aunts.[19] New studies are needed to explain the fact that the index cases do not have the same proportion of aunt similarity in their sisters in this study. When case group boys were examined, it was seen that UH was closer to PAH rather than TH. In the control group boys, UH was found to be significantly superior to TH in estimating PAH. When the groups compared in terms of the effect of consanguineous marriages on SS, similarity of PAH to UH was found to be higher in the case group with a history of consanguineous marriage. Supporting our/investigators' hypothesis, when control groups with and without a history of consanguineous marriages were compared, similarity of PAH to UH was found to be significantly higher in a group with a history of consanguineous marriage.

Limitations

This study has limitations such as restricted number of participants and relatively short follow-up time of participants. A more powerful study with a prospective trial design has to include a larger number of participants. Also for this subject, final height must be investigated so as to achieve statistically more powerful results.

CONCLUSION

In the case of SS, the 'target height' criterion alone is shown to be not reliable in the assessment of genetic compatibility as well as the deviation from PAH. PAH was demonstrated to be statistically similar with AH for girls and with UH for boys. In the presence of consanguineous marriage, the correlation was found to be more pronounced in boys. With these data, it is thought that heights of second- degree relatives can be used as an additional criterion in the estimation of final height, especially in case of non-pathological short stature.

Ethics Committee Approval: The study was approved by local Ethics Committee of study hospital (Ethics Committee approval number: 260/2009.06.25).

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Original Article

Prevalence of Allergic Rhinitis and Risk Factors in School Children

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ABSTRACT

Objective: *To evaluate the prevalence and the risk factors of allergic rhinitis in a particular area.*
Methods: *The main study group consisted of all school children in Kemalpasa district aged 13-14 years. Children with current rhinitis based on responses given in ISAAC questionnaire survey were further evaluated for confirmation. Parents responded to a more detailed questionnaire about allergic diseases and risk factors. Then peak nasal inspiratory flow (PNIF) was evaluated to objectively assess nasal patency. Skin-prick test was performed for ten common allergens.*
Results: *The questionnaire was answered by 90.8% (1373) of children. The prevalence of physician-diagnosed AR was 11.1%. Current rhinitis was found to be 31.3%. Of this group, 55.0% were admitted for the parent questionnaire and tests. Precisely, 90.3% of children accepted PNIF evaluation, and %10.1 of them had a nasal obstruction. Skin-prick tests revealed allergy for at least 1 allergen in 16.6% of children. The present study showed that the children with maternal allergic rhinitis history had 2,18 fold, and the children with seasonal allergic rhinitis had 2,11 fold higher possibility of sensitization to an allergen. The probability of perennial allergic rhinitis was 3,1 fold higher in the children who had siblings with allergic rhinitis.*
Conclusion: *We included all children in a specific age group living in an area in our survey. As well as we found the prevalence of current rhinitis with the ISAAC questionnaire; we also evaluated peak nasal inspiratory flow and used skin-prick tests that yielded objective results.*

INTRODUCTION

Allergic rhinitis (AR) is a global health problem with high prevalence, chronicity, and the burden that imposes on individuals and society. Its estimated worldwide prevalence is 10-25%. The incidence rates of AR and asthma have increased since the 1960s in Western and middle-income countries.[1] Although it is not a fatal disease, it reduces the school performance and quality of life in children.[2] The social and economic costs are striking due to the effects on social life, school performance, and sleep quality.[3] Additionally, its coexistence with asthma is frequently seen.[4] Previous studies regarding risk factors of AR are the presence of any atopy history in the family, maternal smoking, indoor exposure to allergens, >100 IU/mL levels of IgE before age 6, and the presence of allergic specific IgE.[5] Allergic Rhinitis is divided into two subcategories (seasonal and perennial) according to the duration of the symptoms. Mold, dust mites, and animals are the perennial triggers since they present year-round. Pollens of trees, grass, and weed species are seasonal triggers as they exist in a certain period of the year.[6]

The "International study of Asthma and Allergic Diseases in Childhood" (ISAAC) questionnaire survey has been designed to standardize the epidemiological studies. The first phase was designed to determine the prevalence of allergic diseases. The phase I questionnaire was translated into Turkish, and its validity and reliability were proven by previous studies.[7-9] A questionnaire, which was conducted on the parents in the second part of the study, was formed to investigate the reasons for variations in prevalences in ISAAC phase I. Studies using the ISAAC method on the prevalence of allergic rhinitis have been conducted through sampling due to the difficulty of applying them on all children in a region.[10-12] Hence, we aimed to identify prevalence of allergic rhinitis in a group of children at the same age and environment and define the risk factors of seasonal, and perennial allergic rhinitis.

MATERIAL and METHODS

a) Selection of samples and method of questionnaire

The present study was performed in Kemalpaşa in 2012, in accordance with the ISAAC phase I studies. Kemalpaşa is a major industrial district of İzmir, which is the third-largest city in Turkey. There are five elementary schools in the district center, and all 13-14-year-old students were given the ISAAC phase I questionnaire forms. Rhinitis symptoms were investigated based on a positive answer to the following questions: *i)* "ever rhinitis" was defined as a positive response to "have you ever had a problem with sneezing or a runny or blocked nose when you did not have a cold or the flu, *ii)* "current rhinitis" symptoms were evaluated as getting a positive answer to "in the past 12 months, have you ever had a problem with sneezing or a runny or blocked nose when you did not have a cold or the flu". Students with symptoms occurring only between March and October were classified as having "seasonal rhinitis," whereas, students with symptoms occurring throughout the year were classified as having "perennial rhinitis".[13]

Children with current rhinitis and their parents were invited to the Kemalpaşa Health Center in the second part of the study. Some of the children accepted the invitation and came for further investigation with their parents. Parents were given another questionnaire form regarding allergic rhinitis which was expanded with demographic questions including the socio-economic status of the family. The questions concerning allergic rhinitis were: *i)* in the past 12 months, has your child ever taken a medication for the symptoms of allergic rhinitis, *ii)* in the past 12 months, has your child ever treated with immunotherapy for allergic rhinitis, *iii)* how do you classify your child's severity of symptoms; mild-, or moderate-severe intensity. A scale, by Boratav and Belek, was applied to the parents to evaluate their socio-economic status. Mothers and fathers categorized into three groups according to their scores concerning their levels of education: *i)* illiterate, or literate but did not graduate from a primary school (Level-1, 1 point), *ii)* graduated from a primary school (Level-2, 2 points), *iii)* graduated from a middle school or beyond (Level-3, 3 points). The socio-economic classification was made on the occupations of household members: *i)* the parents who were working in their own or someone else's business as lower- or mid-level workers were categorized on higher socio-economic status (high, 3 points), *ii)* the parents who were working as a white-

collar worker, or owned a small business with blue-collar workers were categorized on middle socio-economic status (middle, 2 points), *iii)* the parents who were unskilled day laborers, or unemployed were categorized on lower socio-economic status (Low, 1 point).[14,15]

b) Skin Prick Test

The skin prick test was administered to the children with current rhinitis for Dermatophagoides pteronyssinus, Dermatophagoides farinae, Alternaria alternata, cats, a grass mixture (Phleum pratense, Poapratensis, and Avena eliator), a tree mixture (Betula verrucosa, Alnus glutinosa, and Coryllus avellena), Olea europa, Blatella germanica, histamine, and negative controls. Standardized core allergen extracts and controls were provided by ALK-abello, Horsholm, Denmark. The administration of the allergen extracts is ensured by a prick test device on the volar surfaces of both forearms. The results were evaluated after 15 minutes. When the mean wheal diameter was larger than 3 mm compared to the negative control, the result was accepted as positive.[16]

c) Peak nasal inspiratory flow (PNIF)

Nasal peak flow meter is a device that determines the nasal obstruction with 80% specificity, 77% sensitivity, and 75% accuracy.[17] Nasal peak flow meter (In-Check, HS Clement Clarke International) was utilized to measure the PNIF of the children with current rhinitis. The device was disinfected with 70% alcohol after each use. PNIF values obtained in our study were interpreted to the percentile values of Turkish children by age, which was previously determined by Can et al.[18], and below the 50th percentile was accepted as nasal obstruction. The study design is shown in Table 1.

Table 1. Stages of the present study

1.	Defining children with Current Rhininits using ISAAC Phase One
2.	Children with current rhinitis were invited to the family physicians office with their families.
3.	Parents were given detailed family interview (ISAAC Phase Two Questionnaire and sociocultural status scale)
4.	Administered to all particiants: SPTs and PNIF

d) Statistical analysis

Social Sciences Statistics Package for Windows (SPSS Inc., Chicago) 21 package program was used for statistics of the study. The Kolmogorov-Smirnov test was applied to quantitative data to detect conformity to the normal distribution, and values were stated as median and interquartile range. Mann-Whitney U test and independent-sample t-test were used in the analysis of quantitative data. The chi-square test was applied to compare the categorical variables between groups, and the Fischer test was used when the chi-square test was inappropriate. Binary logistic regression was applied to assess the risk analysis. A value of $p<0.05$ was accepted as statistically significant.

e) Ethical issues

The study protocol was approved by the local ethics committee (27.09.2012/52) and followed the principles for human investigations outlined in the Second Declaration of Helsinki. Informed consent was taken from the guardians of the children. Permissions from the central and provincial directors of the Ministry of Education and town governors were obtained.

RESULTS

The total number of students in Kemalpaşa district was 1511. The ISAAC phase I questionnaire was answered by 1373 (90.8%) of the students. According to the ISAAC phase I questionnaire scores, the rates of ever rhinitis, current rhinitis, allergic rhino-conjonctuvitis, physician-diagnosed AR, seasonal AR, and perennial AR were 503 (36.6%), 430 (31.3%), 304 (22.1%), 153 (11.1%), 117 (8.5%), 230 (16.7%), respectively (Table 2). However, 277 (20.1%) students, who accepted the invitation and further investigation, could be included in the second part of the study.

Table 2. Results of ISAAC phase I questionnaire of all 13-14-year-old participants in Kemalpaşa district (n=1373)

	n	%
Ever rhinitis	503	36.6
Current rhinitis	430	31.3
Allergic rhino-conjonctuvitis	304	22.1
Physician-diagnosed allergic rhinitis	153	11.1
Seasonal allergic rhinitis	117	8.5
Perennial allergic rhinitis	230	16.7

Table 3. Results of second part of the study (n=277)

Features	n (%)
Male	71 (25.6)
Female	206 (74.4)
Symptomatic treatment	100 (36.1)
immunotherapy	6 (2.2)
Mild-symptoms	191 (69)
Moderate-severe symptoms	72 (26)
A positive history of migration	191 (69)
The education level of mothers	
Level-1	43 (15.5)
Level-2	181 (65.3)
Level-3	49 (17.7)
The education level of fathers	
Level-1	10 (3.6)
Level-2	154 (55.6)
Level-3	109 (39.4)
Socio-economic statusstatus	
Low	33 (11.9)
Middle	203 (73.3)
High	37 (13.4)
Monthly income	
<Minimum wage	22 (7.9)
Minimum wage-2x minimum wage	177 (63.9)
>2x Minimum wage	70 (25.3)
Duration of breastfeeding	
None	14 (5.1)
Less than 6 months	34 (12.3)
More than 6 months	224 (80.9)
Weaning	
Before 6 month-old	41 (14.8)
After 6-month-old	230 (83)
Seasonal AR	66 (23.8)
Perennial AR	169 (61)
AR history in any family member	74 (26.7)
AR history in mother	44 (15.9)
AR history in father	20 (7.2)
AR history in the sibling	36 (13)
Children with sensitization to an allergen	46 (16.6)

Therefore, 277 (female: 206, 74.4%) parents answered the questionnaires regarding allergic rhinitis and socio-economic status. According to the parents' answers in the second part of the study, symptomatic treatment and immunotherapy rates were 100 (36.1%) and 6 (2.2%), respectively. Thirty (10.8%) parents did not answer the question regarding the treatment history. One hundred and ninety-one (69%) children had mild, and 72 (26%) children had moderate-severe rhinitis symptoms. Responses of 14 (5.1%) parents were insufficient to assess the symptom severity of their children. The distribution of respective education levels of mothers and fathers were as follows; illiterate, or literate but did not graduate from a primary school (Level-1) (n=43, 15.5% vs n=10, 3.6%), primary school graduates (Level-2) (n=181, 65.3% vs n=154, 55.6 %), secondary, high school or university graduates (Level-3) (n=49, 11.7% vs n=109, 39.4%). The most of the families were categorized in middle socio-economic status (n=203, 73.3%), the remaining were in higher (n=37, 13.4%), and lower (n=33, 11.9%) socio-economic status. As we browse through the rates of atopy history for families; 23 (8.3%) mothers had asthma, 44 (15.9%) had AR, and 7 (2.5%) had eczema. Eight (2.9%) fathers had asthma, 20 (7.2%) had AR, and 6 (2.2%) had eczema. Eight (2.9%) children had a sibling with asthma, 36 (13%) had a sibling with AR, and 7 (2.5%) had a sibling with eczema. One hundred and fifty-five (56.3%) children had a history of exposure to passive smoking. Sixty-nine (24.9%) children had a previous diagnosis of AR made by a physician (Table 3).

Peak nasal inspiratory flow evaluation was accepted by 250 (90.3%) children, and results of 28 (10.1%) children were compatible with severe nasal obstruction. According to the skin-prick test results, 56 (16.6%) children had sensitization to at least one allergen. Household mites (Dermatophagoides pteronyssinus and Dermatophagoides farinea), grass polen and cockroach were the most frequent allergens seen. The distribution of skin-prick test results was summarized in Table 4. There were no significant differences between children with and without sensitization to an allergen in terms of age, gender, socio-economic status, duration of breastfeeding, weaning time, and the educational levels of parents. However, the presence of maternal AR history was significantly higher in patients with sensitization to an allergen (p=0.039) (Table 5). There were no significant differences between the children with seasonal and perennial AR in terms of demographical features. Having a sensitization to an allergen was more frequent in children with seasonal AR than in

Table 4. The distribution of the skin-prick test results (n=277)

Allergen Extracts	n	%
Dermatofoides Farinea	27	9.8
Dermatofoides Pteronysinus	20	7.2
Mold	2	0.7
Cat	5	1.8
Olea Europaea	7	2.5
Trees	4	1.4
Grass	16	5.8
Cockroach	12	4.3

children with perennial AR (Table 6). The univariate logistic regression model demonstrated that the presence of seasonal AR (OR: 2.11, 95% CI:1.08-4.10) and maternal AR (OR:2.18, 95% CI:1.02-4.65) were the risk factors for having a sensitization to at least one allergen (Table 7). The logistic regression model showed that having a sibling with AR was a risk factor for perennial AR (OR: 4.44, 95% CI: 1.37-4.36, Table 8).

Table 5. The comparison of the demographical features between children with and without sensitization to an allergen (n=277)

Features	Children without sensitization to an allergen	Children with sensitization to an allergen	p-value
Age (mean ± SD)*	13.6±0.64	13.43±0.54	0.058
Male n (%)** Female n (%)**	56 (24.2) 175 (75.8)	15 (32.6) 31 (67.5)	0.235
A positive history of migration n (%)**	158 (69.3)	31 (67.4)	0.742
The education level of mothers n (%)** Level-1 Level-2 Level-3	 41 (18) 147 (64.5) 40 (17.5)	 2 (4.4) 34 (75.6) 9 (20)	0.074
The education level of fathers n (%)** Level-1 Level-2 Level-3	 9 (3.9) 125 (54.8) 94 (41.2)	 1 (2.2) 29 (64.4) 15 (33.3)	0.852
Socio-economic status n (%)** Low Middle High	 31 (13.6) 166 (72.8) 31 (13.6)	 2 (4.4) 36 (80.0) 7 (15.6)	0.413
Monthly income n (%)** <Minimum wage Minimum wage-2x minimum wage >2x Minimum wage	 20 (8.9) 144 (64.3) 60 (26.8)	 2 (4.4) 33 (73.3) 10 (22.2)	0.592
Number of siblings (mean ±SD)*	2.53±1.96	2.15±1.21	0.425
Duration of breastfeeding n (%)** None Less than 6 months More than 6 months	 11 (4.8) 29 (12.8) 187 (82.4)	 3 (6.7) 5 (11.1) 37 (82.2)	0.852
Weaning n (%)** Before 6-month-old After 6-month-old	 34 (15) 192 (85)	 7 (15.6) 38 (84.4)	0.621
Seasonal AR n (%)**	54/231 (23.4)	18/231 (39.1)	**0.026**
Perennial AR n (%)**	151/231 (65.4)	18/231 (39.1)	**0.001**
AR history in any family member n (%)**	57 (24.9)	17 (37.8)	0.089
AR history in mother n (%)**	32 (14,0)	12 (26.7)	**0.039**
AR history in father n (%)**	15 (6.6)	5 (11.1)	0.299
AR history in the sibling n (%)**	29 (12.7)	7 (15.6)	0.632

Mann-Whitney U test and independent-sample t-test were used in the analysis of quantitative data. The chi-square test was applied to compare the categorical variables between groups, and the Fischer test was used when the chi-square test was inappropriate.
AR: Allergic Rhinitis, SD: Standard deviation; AR: Allergic Rhinitis
** Normally distrubuted data were given as mean ± SD (Independent-samples t test)*
*** The chi-square test was applied to compare the categorial variables between groups, and the Fischer test was used when the chi-square test was inappropriate*

Table 6. The comparison of the demographical features between children with seasonal AR and perennial AR (n=277)

	Seasonal AR	Perennial AR	p-value
Age (mean ±SD)*	13.6±0.60	13.54±0.65	0.503
Male n (%)** Female n (%)**	18 (27.3) 48 (72.7)	38 (22.5) 131 (77.5)	0.439
Positive history of migration n (%)**	141 (69.1)	50 (71.4)	0.932
The education level of mothers n (%)** Level-1 Level-2 Level-3	 8 (12.3) 41 (63.1) 16 (24.6)	 31 (18.6) 109 (65.3) 27 (16.2)	0.232
The education level of fathers n (%)** Level-1 Level-2 Level-3	 8 (4.0) 113 (55.9) 25 (13.6)	 2 (2.8) 41 (57.7) 28 (39.4)	0.231
Socio-economic status of the family n (%)** Low Middle High	 27 (13.3) 151 (74.4) 25 (13.6)	 7 (9.9) 51 (71.8) 13 (13.6)	0.188
Monthly income n (%)** <Minimum wage Minimum wage-2x minimum wage >2x Minimum wage	 16 (8) 135 (67.5) 49 (24.5)	 8 (11.3) 42 (59.2) 21 (29.6)	0.402
Number of siblings*	2.43±1.67	2.15±1.21	0.425
Duration of breastfeeding n (%)** None Lessthan 6 months Morethan 6 months	 5 (7.8) 8 (12.5) 51 (79.7)	 8 (4.8) 20 (12) 139 (83.2)	0.660
Weaning n (%)** Before 6 month-old After 6-month-old	 9 (14.1) 55 (85.9)	 23 (13.9) 143 (86.1)	0.963
AR history in any family member n (%)**	19 (28.8)	46 (27.4)	0.829
AR history in mother n (%)**	16 (24.2)	22 (13.1)	0.037
AR history in father n (%)**	6 (9.1)	12 (7.1)	0.615
AR history in the sibling n (%)**	4 (6.1)	28 (16.7)	0.034

SD: Standard deviation; AR: Allergic Rhinitis
**Normally distrubuted data were given as mean ± SD (Independent-samples t test)*
***The chi-square test was applied to compare the categorial variables between groups, and the Fischer test was used when the chi-square test was inappropriate*

DISCUSSION

The major findings of the present study were: *i)* according to the student's answers the prevalence of current rhinitis was 31.3%, physician-diagnosed AR was 11.1%, allergic rhino-conjunctivitis was 22.1%, *ii)* house dust mites (Dermatophagoides pteronyssinus and Dermatophagoides farinea), grass pollens, and cockroach were the most frequent allergens, *iii)* the presence of maternal AR history was significantly higher in patients with sensitization to an allergen than in patients without sensitization to an allergen, *iv)* the frequency of having a sensitization to an allergen was significantly higher in children with seasonal AR than in children with perennial AR *v)* having a sibling with AR was a risk factor for perennial AR.

The number of epidemiological researches on AR is

Table 7. Risk factors of having a sensitization to an allergen (n=277)

		95% Confidence Interval		
Children with sensitization to an allergen/ Children without sensitization to an allergen	**O.R.**	**Lower Limit**	**Upper Limit**	**p-value**
AR history in mother	2.18	1.02	4.65	0.043
Seasonal AR	2.11	1.08	4.10	0.028
Perennial AR	0.34	0.18	0.65	0.001

Logistic Regression- Univariate Model

Table 8. Risk analysis of seasonal and perennial allergic rhinitis (n=277)

		95% Confidence Interval		
Seasonal AR/ Perennial AR	**O.R.**	**Lower Limit**	**Upper Limit**	**p-value**
AR history in mother	0.47	0.23	0.97	0.040
AR history in sibling	3.10	1.04	9.22	0.042
D. farinea	0.35	0.14	0.88	0.026

Logistic Regression- Univariate Model

inadequate to specify the disease prevalence and its burden. Additionally, the answers may vary based on the awareness of the population concerning allergic diseases especially in questionnaire-based studies.[19] In addition, the prevalence of allergic rhinitis varies according to the age group of the children. In the ISAAC Phase I Study, the prevalence of AR among 13-14-year-old children, was reported with a wide range between 1.4% and 39.7%.[20] According to an ISAAC phase III study results, the prevalence of rhinoconjunctivitis was 8.5% among 6-7-year-old children.[21] In a meta-analysis by Kalmarzi from Iran, the prevalence of AR was 18% in children, and 25% in adolescents.[22] In an ISAAC-based questionnaire study from Budapest including 3836 6-12-year-old children, it was reported that the prevalences of current rhinitis, physician-diagnosed AR, and current allergic rhino-conjunctivitis were 29.3 %, 9.7 %, and 16.2%, respectively.[23] In the current study, we reported the prevalence of current rhinitis, physician-diagnosed AR, and allergic rhino-conjunctivitis as 31.3%, 11.1%, and 22.1%, respectively.

Several allergic rhinitis prevalence studies using the ISAAC questionnaire were made in Turkey. Kuyucu et al.[24] reported that the prevalence rates of ever rhinitis, current rhinitis, and ever hay fever were 36.3%, 30.6%, and 8.3%, respectively among 9-11-year-old children in 2006. Civelek et al.[13] reported the prevalence of rhino-conjunctivitis as 23.5% in 2010. Tamay et al.[25] reported the rate of current rhinitis as 29.2% by using ISAAC questionnaire among 6- to 7-year-old children in 2014. In a study that included 396 preschool children from Mersin, Turkey, the prevalence of ever rhinitis, current rhinitis, and physician-diagnosed allergic rhinitis were 41.7%, 38.6%, and 13.4%, respectively. Demir et al.[27] reported that the prevalence of rhinitis among children aged 5-18 years rises from 4.6% to 13.6% in the Agean region of Turkey. Kemalpaşa is in Turkey's Aegean region. Studies conducted in the same region show that the prevalence of rhinitis is increasing.

As allergens, grass pollens and house dust mites has been frequently reported as etiologic agents in AR among adults and children. Şahin et al.[28] evaluated the skin prick test results in 1200 adults and children who were diagnosed with AR. It was found that house dust mites were the most frequent allergens. Kuyucu et al.[24] reported a higher sensitization rates caused by grass pollens, mites, and cockroaches from Turkey. Özkars et al.[29] retrospectively evaluated aeroallergen sensitivity in children, aged between 1-16 years in the Province of Kahramanmaraş. It was

found that grass pollens and house dust mites were the most frequent allergens. In the current study, house dust mites, grass pollens and, cockroaches were the most frequent allergens which were compatible with the previous reports.

A strong correlation was found between allergic diseases and atopy in some researches.[30,31] However, atopy may not be determined in all allergic patients. This situation may be related to subclinical sensitization.[32] In the present study, 16.6% of the children were allergic to at least one allergen. Performing the skin-prick tests with more allergens might ensure the determination of higher rates of atopy.

Numerous risk factors have been defined for AR and atopy in children. The presence of a family history of allergic diseases, male gender, birth during the pollen season, early-life antibiotic use, maternal smoking, exposure to indoor allergens, and serum IgE levels higher than 100 IU/mL before age 6 were considered as risk factors for AR.[5,32,33] Wang et al.[34] investigated the relationship between maternal AR and the allergic diseases of the children. They found that the rate of allergic diseases in children was significantly higher in the presence of coexistence of maternal AR and asthma than in the presence of maternal AR only. Kuyucu et al.[24] suggested that family atopy, heating with gas stove and the presence of dampness/molds at home during the first year of life were the risk factors for current AR. Batlles-Garrido et al. proposed that atopy, cat contacts at home during the first year of life, prior diagnosis of asthma, nocturnal cough in the absence of cold, the presence of maternal or paternal AR history, wheezing at any time, and nursery school attendance were the risk factors for AR.[35] Several studies have emphasized the existence of phenotype-specific genes for atopy. Additionally, it is known that the impact of the maternal phenotype is stronger than the paternal phenotype.[36] Edenharter et al.[37] showed that higher levels of cord blood IgE levels may have a role in the prediction of early sensitization but not for airway or skin symptoms. According to some researchers, the decline in the exposure to infections during the first year of life is considered an immunologic risk factor for atopy. The postulated mechanism is the fact that some infections induce a systemic and nonspecific switch to TH1 activities which may lead to inhibition of the development of atopy during childhood.[38] The present study showed that seasonal AR and the presence of maternal AR history were the risk factors for atopy.

Only a few studies have been performed regarding differences between seasonal and perennial AR in terms of the presence of atopy and family history of allergic diseases. Sibbald et al.[39] performed a questionnaire-based study to evaluate the symptoms, atopic state, and medical history of people with seasonal and perennial AR. The results revealed that 113 of subjects were without rhinitis, 51 had seasonal symptoms alone, 128 had perennial symptoms alone, 131 had perennial symptoms with seasonal exacerbations. Atopy rates, history of eczema, and the presence of a family history of allergic disease were significantly higher in the seasonal AR group. In a study by Mısırlıoğlu et al.[40], no significant differences were found between seasonal and perennial AR, in terms of family history of atopy. In the present study, the rates of AR history in mothers were significantly higher in the seasonal AR group than in the perennial AR group. Additionally, logistic regression analysis showed that AR history in a sibling was a risk factor for perennial AR. This condition can be explained by genetic susceptibility. Additionally, living in the same environment may have given rise to exposure to similar allergens and microorganisms.

Fuller et al.[41] performed a study to evaluate the nasal patency with PNIF and nasal obstruction symptom evaluation (NOSE) scale to assess the outcomes of functional septorhinoplasty. Although they found a weak correlation between PNIF results and NOSE scores, PNIF demonstrated the amelioration of nasal patency after rhinoplasty. Prescott et al.[42] suggested that PNIF values increased with height and weight in childhood. Since the maximal nasal inspiratory effort should be made during the PNIF assessment, and the degree of cooperation of the child is important.In the present study, only 10.1% of the children in the second part of the study, PNIF results were compatible with nasal obstruction. These results may be related to the difficulty of obtaining maximum cooperation

while performing PNIF assessment in large groups. The limitation of the questionnaire-based determining the participants in the second part of the study might also have contributed to the inconsistency of the PNIF results.

Our study has several limitations. Maybe, some children might have erroneously selected the "yes" option of the question "have you experienced rhinorrhea, nasal obstruction, or sneezing when you have not had a cold, in the past 12 months" as a handicap of the questionnaire-based study. In the current study, detection of higher rates of children without sensitization to an allergen can be explained partly by this situation. However, this limitation was tried to be corrected with applying family questionnaires. Secondly, all of the children who were categorized as patients with current rhinitis according to the ISAAC phase I questionnaire could not be included in the study group, since only 55% of them applied to the physician's office.

CONCLUSION

In conclusion, including all children of the same age and the same environment is a valuable epidemiological aspect of the present study. Applying the family questionnaires could have decreased the false-positive cases with current rhinitis. Seasonal AR and the presence of maternal atopy history are the risk factors for having a sensitization to at least one allergen. Having a sibling with AR is a risk factor for perennial AR.

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Original Article

Domestic Lifestyle and Nutritional Status of Children During Covid-19 Pandemics

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ABSTRACT

Objective: *After Covid-19 pandemic was declared, a number of restrictions have been imposed all over the world. We aimed to detect changes in eating habits of children and adults during Covid-19 pandemic when lifestyle changes were inevitable due to these restrictions.*
Methods: *This is a descriptive cross-sectional study. The data collection process was completed by online questionnaire forms sent via mail system. There were questions about demographic characteristics of the participants and their children, lifestyle changes during the pandemic period and awareness of the pandemic. Participants with more than one child were asked to use the information of their youngest children. In statistical analyzes we used "Statistical Package for Social Science" (SPSS) 20.0 for Windows. Pearson Chi-square test was used for comparisons of categorical variables. The significance level was accepted as p≤ 0.05 in all statistical processes.*
Results: *A total of 327 people between 19-65 years of age participated in this study, and 174 of them had children with a mean age of 6.8 years, including 96 (55.7%) boys and 78 (44.3%) girls. Among all children, physical activity decreased in 101 (58%), screen time increased in 87 (50%) and 40 (23%) of them consumed their meals in front of the screen. The snacking habits of 130 (74.8%) children increased, 34 (19.5%) started consuming too much junk food and 12 of them (6.9%) gained weight. We observed that boys consumed more food than girls during their stay at home when compared to usual prerestriction days as they felt anxious and troubled (p=0.02).*
Conclusion: *Pandemics do not affect our lives not only with disease burden but also, have effects on daily lives of families and children. During this period, besides precautions against infection, special interest should be given to feeding, sleeping habits and physical activities that would boost immune system and measures should be taken to prevent harmful habits.*

INTRODUCTION

In December 2019, the SARS-Cov 2 virus from the coronavirus family, thought to have spread from a seafood market in Wuhan Province of China, caused a worldwide pandemic.[1,2] This virus was later called as Covid-19. After Covid-19 pandemic was declared by the World Health Organization (WHO), a number of restrictions have been imposed all over the world in order to prevent the spread of the virus.[3] Changes in normal life patterns such as social life restrictions, flexible working hours, school closing and strict hygienic quarantine practices increased anxiety, stress and depression levels among adults and children.[1] Therefore, tendency of peoples to consume high-sugar foods and alcoholic beverages increased in order to feel good. Besides, the consumption of packaged products was also increased due to the concerns that there would be food shortages that might cause deficiencies in the intake of essential nutrients such as vitamins and minerals.[4]

There is a two-way relationship between infections and nutritional status. People with nutritional

disorders have greater risk of having infections, more severe course of the disease and higher mortality rates. On the other hand, the application of diets enriched with vitamins, minerals and antioxidants significantly reduces the rate of immune system problems and related disorders.[5,6] All age groups are susceptible, but people with comorbidities or the elderly are more likely to develop a severe form of the covid-19 infection. Although children seem to have less severe clinical symptoms when infected.[5,7] The potential harm of this novel disease in children with nutritional disorders remains largely unknown. Therefore, keeping the nutritional status of children balanced during pandemics is crucial.

Besides the relation between the infection and nutritional status, staying at home for longer periods of time increased the incidence of eating disorders such as binge eating behavior, decreased physical activity and sleep disturbances among the children.[8-10] This brought the danger of increased risks of stress, nutritional disorders and various chronic diseases.[4,5] In this period, children staying at home may face nutritional problems such as malnutrition, nutritional deficiencies, overnutrition and obesity. However, on the other hand, children who are with their family for 24 hours at home may be eating healthier food as they do not have the opportunity to choose their own choice of food, as they were outside. This study was planned to determine the nutritional disorders such as anorexia, excessive eating, and excessive consumption of junk food in children and adults who stayed at home during the Covid-19 quarantine period.

MATERIALS and METHODS

This is a descriptive cross-sectional study which was conducted between June and July 2020 after the approval of Ministry of Health General Directorate of Health Services, Covid-19 Scientific Research Evaluation Commission and Kırıkkale University Non-Interventional Ethics Committee. Data were collected by using a questionnaire that was prepared by the researchers after a literature search. The questionnaire forms consisted of 47 questions on demographic characteristics of the participants, lifestyle changes during the pandemic, awareness on Covid 19 pandemic and nutritional status of breastfeeding babies.

No sampling method was used and the data collection was completed online by using snowball method sending questionnaires via e-mails to the people that the researchers were familiar with. Study participants filled out the questionnaire forms, and accepted to participate in the study. The inclusion criteria were being older than 18 years, and the forms had to be completed entirely and sent back to us. We did not consider the incomplete forms. The presence of Covid-19 infection in the participants or their families was not inquired. Participants with more than one child were asked to use the information of their youngest child. A total of 1204 questionnaire forms were sent and only 327 (27.16%) of them were returned.

For statistical analyzes “Statistical Package for Social Science” (SPSS) 20.0 for Windows was used. Pearson Chi-square test was used for comparisons of categorical variables. Calculations of frequency and percentage were used for the statistical analysis of the data. The significance level was accepted as $p \leq 0.05$ in all statistical analyses.

RESULTS

Demographic characteristics and Covid-19 awareness of the participants

A total of 327 participants between the ages of 19-65 years (with a mean age of 33 years) answered the questionnaire forms. Fifty-one (15.6%) participants were male and 276 (84.4%) of them were female, while 116 (35.5%) were single, 211 (64.5%) were married and 174 (53.2%) had at least one child. Most (80.1%) of the participants had associate/bachelor/master/doctorate degrees. Most (n: 275; 84.1%) of the participants stated that they lived with their families, 16 (4.9%) with their friends, 1 (0.3%) with their relatives, and 35 (10,7%) of them lived alone. Based on their medical histories, 38 (11.6%) had a chronic disease. Among all, 212 (64.8%) defined themselves as normal weight, 28 (8.6%) as thin, 62 (19%) as overweight and 25 (7.6%) as obese.

During the pandemic, 249 (76.2%) participants stated that they used social media and 78 (23.8%) television to get information about Covid-19. When the

Table 1. Distribution of communication tools used to get information about Covid-19 by age groups and gender

	18-24 age		25-49 age		50-64 age			
Tool to get information about Covid-19	**n**	**%**	**n**	**%**	**n**	**%**	**χ2**	**p**
Television	7	15.2	63	23.8	8	50	7.912	0.019
Social Media	39	84.8	202	76.2	8	50		

	Female		Male			
Tool to get information about Covid-19	**n**	**%**	**n**	**%**	**χ2**	**p**
Television	69	25	9	17.6	1.281	0.258
Social Media	207	75	42	82.4		

χ^2=Chi-Square, p<0.05

Table 2. Distribution of change in nutritional behaviour according to gender

	Female		Male			
Nutritonal Status	**n**	**%**	**n**	**%**	**χ2**	**p**
Eating Behaviour didn't change	82	29.7	20	39.2	6.466	0.091
Eating Too Much Food (junk food, homemade cakes, pastry)	108	39.1	12	23.5		
Very Poor Appetite, didn't want to eat anything	7	2.5	0	0		
Consuming mostly homemade healthy food	79	28.6	19	37.3		

χ^2=Chi-Square, p<0.05

distribution of the communication tools used by the participants to follow the agenda about Covid 19 was evaluated, we found a statistically significant difference by age groups (p=0.019). There was no statistically significant difference in the use of communication tools between male and female participants (p=0.258) (Table 1).

Two hundred and forty-eight participants (75.8%) stated that they had sufficient knowledge about Covid-19, 76 (23.2%) of them had inadequate information and 3 (0.9%) participants did not have any information about Covid 19 disease at all. Majority [269 (82.3%)] of the participants stated that they had been talking about the Covid-19 pandemic at home and 113 (65%) participants who had children had been talking this issue with their children.

Behavior/lifestyle changes of the participants during pandemic period

During the pandemic, 120 (36.7%) participants stated that their consumption rate of junk food increased, while 102 (31.2%) of them did not change their dietary habits, and 98 (30%) of them were having healthier diet However, 10 (3.1%) participants had a very poor appetite and didn't want to eat anything. We have not observed any statistically significant difference between the genders according to the change in dietary habits (p=0.091) (Table 2).

During the pandemic, 143 (43.7%) participants stated that their sleeping patterns did not change, 94 (28.75%) of them had no certain bedtime, and 53 (16.2%) participants went to bed at a later time than usual and woke up later. When the distribution of the change in sleeping patterns was evaluated, we found a statistically significant difference between genders (p=0.009). Although almost half of the participants in both genders stated that there was no change in their sleeping patterns, women generally stated that they had difficulties in regulating their sleep times, and men went to bed later and woke up later. We observed no statistically significant difference according to the marital status of the participants (p=0.133) (Table 3).

Table 3. Distribution of sleeping patterns according to gender and marital status

	Female		Male			
Sleeping patterns	**n**	**%**	**n**	**%**	**χ2**	**p**
Had no change in sleeping patterns	121	43.8	22	43.1	11.557	0.009
Went to bed too late, gets up early	30	10.9	7	13.7		
Went to bed too late, gets up late	38	13.8	15	29.4		
Time going to sleep was uncertain	87	31.5	7	13.7		
	Married		**Single**			
Sleeping patterns	**n**	**%**	**n**	**%**	**χ2**	**p**
Had no change in sleeping patterns	99	46.9	44	37.9	4.031	0.33
Went to bed too late, gets up early	26	12.3	11	9.5		
Went to bed too late, gets up late	28	13.3	25	21.6		
Time going to sleep was uncertain	58	27.5	36	31		

χ^2=Chi-Square, p<0.05

Table 4. Distribution of physical activity status by gender, marital status and age groups

	Female		Male			
Physical activity status	**n**	**%**	**n**	**%**	**χ2**	**p**
Not changed	149	54	24	47.1	4.960	0.084
Decreased	90	32.6	24	47.1		
Increased	37	13.4	3	5.9		
	Married		**Single**			
Physical activity status	**n**	**%**	**n**	**%**	**χ2**	**p**
Not changed	120	56.9	53	45.7	4.031	0.133
Decreased	66	31.3	48	41.4		
Increased	25	11.8	15	12.9		

	18-24 age		25-49 age		50-64 age			
Physical activity status	**n**	**%**	**n**	**%**	**n**	**%**	**χ2**	**p**
Not changed	13	28.3	149	56.2	11	68.8	14.435	0.006
Decreased	24	52.2	87	32.8	3	18.8		
Increased	9	19.6	29	10.9	2	12.5		

χ^2=Chi-Square, p<0.05

Hundred and fourteen (34.9%) participants mentioned that their daily physical activity decreased during the pandemic, while 173 (52.9%) of them indicated lack of any change in their daily physical activities. On the other hand, 40 (12.2%) participants stated that they started to do regular physical exercise at an increasing rate during this period. Any statistically significant difference was not observed between genders as for rates of physical activities performed (p=0.084) and marital status (p=0.133). However, there was a significant difference in the change in physical activity according to age groups such as; individuals between the ages of 25-49 continued their physical activity during pandemic at the same frequency as before more than the other age groups (p=0.006) (Table 4).

Demographic characteristics and lifestyle changes of the participants' children during pandemic

Hundred and seventy-four (52.3%) participants had at

Table 5. Distribution of eating behaviour of children according to mood by gender

Eating behaviour according to mood	Boy		Girl			
Anxious and Troubled	**n**	**%**	**n**	**%**	**χ2**	**p**
Eating more	33	21.5	10	47.6	7.170	0.02
Eating less	35	22.9	2	9.5		
	Boy		**Girl**			
Bored and have nothing to do	**n**	**%**	**n**	**%**	**χ2**	**p**
Eating more	33	34.4	35	44.9	2.002	0.6
Eating less	17	17.7	12	15.4		
	Boy		**Girl**			
Furious and Angry	**n**	**%**	**n**	**%**	**χ2**	**p**
Eating more	21	21.9	17	21.8	1.135	0.93
Eating less	20	20.8	18	23.1		
	Boy		**Girl**			
Happy	**n**	**%**	**n**	**%**	**χ2**	**p**
Eating more	23	24	22	28.2	1.616	0.44
Eating less	16	16.7	8	10.3		
	Boy		**Girl**			
Unhappy	**n**	**%**	**n**	**%**	**χ2**	**p**
Eating more	16	16.7	15	19.2	0.196	0.90
Eating less	20	20.8	16	20.5		

χ^2=Chi-Square, p<0.05

least one child (max 4-min 1). The mean age of their children including 96 (55.7%) boys, and 78 (44.3%) girls was 6.8 years (min 0-max 32 years). Seven (4.1%) children had a chronic disease. Children over 18 years of age (n=15) were excluded for the rest of the statistical analyses. Mean age of the children under 18 years of age was 4.9 (min 0-max 18) years.

Physical activity of 101 (58%) children decreased, and 80 (48.2%) had a sleep problem. Sleep problems were reported as; going to bed late, difficulty in falling asleep, sleeping alone and waking up frequently at night. Forty-six (55.5%) children with sleep problems were eating much before going to bed.

Parents of 48 (27.5%) children mentioned an increase in their children's body weights. Twelve (6.9%) children were mentioned to gain weight because of eating a lot. The snacking habits of 130 (74.8%) children were increased during this period; 65 (67.3%) had binge eating, and 34 (19.5%) children started consuming too much junk food. Eighty-seven (50%) children had increased screen time, where 40 (23%) children consumed their meals in front of TV/tablet. When the planning of meal times was taken into account, 130 (74.8%) parents preferred family meal hours around the family table and 44 (25.2%) parents let their children decide their meal times.

Among the reasons for overeating in this period, the most marked option was "the boredom of the child who has nothing to do" (39.8%) and among the reasons for eating less "the child being furious and angry" (21.9%) was the most marked option. When we evaluated the effects of changes in children's mood as being angry, happy, unhappy, bored on eating behaviors during pandemic, we could not find any significant difference between genders (Table 5)

(p>0.05). However, we observed a significant difference between genders as for the change in eating behaviors when children felt anxious and troubled (p=0.02). Almost half of the boys consumed more food than normal when they felt anxious and troubled, where there was no change in most of the girls. There was also no statistically significant difference between genders when the relation between the age and its effect on the change in children's mood regarding their eating behaviors (Table 5) (p>0.05).

Nutritional Status of Babies of Nursing Mothers

Fifty-three children of the participants were under age of 2. The babies were fed exclusively with breast milk (n:5: 8,62%), breast milk and complementary food (n:28: 48,28%) and formula and complementary food (n:20; 34,48%). It was stated that 30 (17.2%) babies had not changed their breastfeeding pattern, but 11 (20.7%) had an increase and 7 (13.2%) had a decrease in their breastfeeding frequency during pandemic period.

DISCUSSION

After Covid-19 pandemic was declared, restrictions have been placed on social activities which forced individuals to stay at home and caused a decrease in their physical activities. Along with the increased stress caused by the restrictions, imposed impairments were observed in the eating behavior of individuals.[11] During the pandemic, people received 27% higher calories compared to the same period of the previous year.[12] In our study, 33.6% of the participants stated they ate much more junk food, homemade cakes, pastries and 30% of them consumed more often homemade meals considering them as healthy foods. We found an increase in the consumption of junk food and healthy foods in women, but no significant statistical difference was found between genders. As consistent with our results, a study from Italy revealed that the consumption of junk food and healthy foods increased in women during pandemic, but the authors could not find any relationship between weight and female gender.[13]

Regulations in public life such as home-office work style, distance education system, quarantine practices, closing playgrounds caused a decrease in the physical activities.[4,14] In consistent with the given literature, 34.9% of our study participants mentioned that they have quitted their physical activities during pandemic.

An increase in stress levels, along with changes in eating habits, also leads to sleep problems. It is known that disruptions in nutrition and sleeping patterns negatively affect the immune system.[15,16] A study conducted in Italy showed that sleeping patterns in society were disrupted by quarantine practices compared to previous periods.[17] In a study conducted in China, it was reported that people spend much more time in bed during the pandemic, but duration of sleep decreased. Staying for long hours in front of the screen before sleep disrupts sleep hygiene, causes anxiety and increases sleep problems.[18] As compatible with these results, in our study more than half of the participants had a change in their sleeping patterns during the pandemic period. And we found a statistically significant difference by gender. While women generally had difficulties in regulating sleep hours, men went to bed late and woke up late.

Due to stricter restrictions for children under age of 18 years, they stayed longer than adults at home and we found that 58% of the participants' children had a decrease in their physical activities, and 74.8% of them more often consumed snacks. It is known that reduced physical activity and increased consumption of junk food increase the risk of obesity in adulthood and related diseases.[19] A meta-analysis showed that obesity increases the fatality rate of Covid-19 infection.[20] It is worrying that 27.5% of the parents in our study group reported that their children's weight increased during pandemic period. A study conducted in Canada during the pandemic period showed that closing children's playgrounds and quarantine at home reduced children's physical activity especially in the adolescent group and spending long hours at home caused an increase in screen time of both adolescents and children.[14,21] It has been revealed that if screen time increases, the risk of obesity due to involuntary consumption of junk food increases.[22] Our study also showed that 50% of the children spent long hours staring at a screen and approximately half of these children (45.9%) adopted the habit of

eating in front of the screen.

The quality and quantity of the foods can vary according to our mood states. While we eat less in some mood states, we eat more or prefer foods rich in carbohydrates and fats in other mood states.[23] We evaluated the effects of changes in children's mood state on their feeding behavior during pandemic. In our study, parents mostly said that their children were eating too much because they were bored and have nothing to do. Eventually, they ate less when they were furious and angry. While more than half of the boys ate more when they were feeling anxious and troubled, there was no change in girls' eating behavior in the same situation (Table 5).

As compatible with our results a study from China revealed that during the pandemic period, physical activity decreased in children, negative effects on their mood increased, where boys were more affected.[24] A study from United Kingdom also showed that negative mood state was associated with reduced physical activity and binge eating.[25] Therefore, we can conclude that, pandemic had a negative impact on children's eating behaviors because of social isolation and lack of physical activity.

Limitations of the study

We used self- assessments of the participants about their and their children's life style changes, and we didn't use psychometric scales or anthropometric measurements.

CONCLUSION and SUGGESTIONS

Quarantine precautions implemented to prevent Covid-19 spread affected children more than adults. Due to interruption of education in schools and prolonged curfews for under-18s, forced children spend most of their time at home. Their physical activities and sleeping hours decreased, in contrast, time spent for watching TV, and/or surfing on internet, and eating in front of the screen increased. With these changes increase in the risk of obesity is inevitable. Therefore, during the pandemic period, not only precautions should be taken against infection, but also nutrition, sleep and physical activities which boost immune system should be kept at optimal levels and measures should be taken to prevent resorting to harmful habits.

Ethics Committee Approval: We have the approval of Ministry of Health General Directorate of Health Services, Covid-19 Scientific Research Evaluation Commission and Kırıkkale University Non-Interventional Ethics Committee (Ethics Approval: 26.08.2020; numbered 2020.07.13).

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Original Article

The Factors Affecting The Efficiency of Continuous Ambulatory Peritoneal Dialysis in Children

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ABSTRACT

Objective: *Peritoneal dialysis is a complex and variable process. Many factors can affect efficiency of dialysis, and relevant mortality and morbidity rates. Efficient dialysis is important in improving quality of life as well as reducing the morbidity and mortality rates. Dialysis fill volume, intraperitoneal pressure and ultrafiltration (UF) are important variables that determine dialysis efficiency. We aimed to investigate the factors affecting dialysis efficiency and to determine necessities to develop a more effective dialysis program.*

Methods: *Sixteen continuous ambulatory peritoneal dialysis (CAPD) patients between the ages of 7 and 19 years who were followed up in the Pediatric Nephrology Department were included in the study. Patients who had peritonitis, surgical or medical complications in the last 6 months were excluded from the study. Demographic data, duration of dialysis, hemogram, urea, creatinine, albumin, glucose levels, intraperitoneal pressures, peritoneal equilibration test (PET) and Kt/Vurea test results were recorded.*

Results: *Mean Kt /Vurea, dialysis fill volume, UF, intraperitoneal pressure, Hb and serum albumin were found as 2.5±0.93 (1.22-4.64), 1123.4±126.86 (875-1360) ml/m2, 600.1±382.15 (85 -1375) ml, 12.9±2.77 (8.5-19) cm/H2O, 9.0±1.54 (6.3-11.8) gr/dl and 3.6±0.61 (2.45-4.8) gr/dl, respectively. A statistically significant relationship was shown between UF and Kt/Vurea (p=0.04). The mean duration of dialysis was 54±36 months. The majority of the cases had high (37.5%) and medium-high (31.25%) peritoneal permeability. High permeability was found to have a significant relationship with the duration of dialysis (p=0.04).*

Conclusion: *Efficient peritoneal dialysis depends on preserved ultrafiltration. Therefore, the dialysate volume should be calculated according to the intraperitoneal pressure and dialysis should be adjusted according to the permeability properties of the peritoneal membrane.*

INTRODUCTION

The first application of dialysis in humans was carried out by the German scientist Genter in 1923.[1] Peritoneal dialysis (PD) was first performed on children in 1978 by Oreopulos et al. and started to be used in the treatment of chronic renal failure (CRF).[2]

Peritoneal dialysis is the most common, and increasingly used renal replacement therapy in the world for children with CRF until the introduction of renal transplantation procedure.[3] This method of treatment is increasingly used in the world and in Turkey.[4,5] The principle of peritoneal dialysis is based on the fact that the peritoneum is a semipermeable membrane similar to the hemodialysis filter. This method is based on the passage of toxic substances into the fluid delivered into the peritoneal cavity and then evacuation of this fluid.[6]

Peritoneal dialysis is a complex and variable process. Many factors can affect efficiency of dialysis, and related mortality, and morbidity rates. Studies have pointed out that intraperitoneal pressure can affect dialysis adequacy and ultrafiltration. Intraperitoneal pressure measurement is a valuable parameter in determining the optimal fill volume, which is very

important for peritoneal dialysis adequacy.[7] Based on this, our study aimed to investigate the factors affecting intraperitoneal pressure, the effects of ultrafiltration, residual renal functions and type of peritoneal permeability on dialysis adequacy, and what should be done to prescribe more effective dialysis.

MATERIAL and METHOD

Sixteen continuous ambulatory peritoneal dialysis (CAPD) patients between the ages of 7 and 19 years who were followed up in the Pediatric Nephrology Department were included in the study. Local ethics committee approval was obtained. Patients who had peritonitis, surgical or medical complications in the last 6 months were excluded from the study. Demographic data, drugs used, primary diagnoses and dwell times of dialysis of the patients were recorded. Hemogram, urea, creatinine, albumin and glucose values were recorded. Peritoneal equilibration (PET) and Kt/Vurea screening tests were used in first month, then every 6 months. Measurements of intraperitoneal pressure, PET and Kt/Vurea were performed, and the results were described in detail
Intraperitoneal pressure measurement: Patients are placed on their back after their bladder is emptied. The peritoneal dialysis system is connected, all fluid is drained and the specified volume of peritoneal dialysis fluid is given. Peritoneal dialysis tube is fixed in an upright position. The ruled column is held so that the zero point is on the mid-axillary line, at the center of the abdominal cavity. The connection path to the patient is opened. The height of the column where the dialysis fluid is located is measured in centimeters during inspiration and expiration, and its arithmetic average is calculated.[7,8] It has been shown that the intraperitoneal pressure measured through the intravesical catheter is equivalent to the pressure measured through the peritoneal catheter while the patient is lying supine.[9] In our study, measurement procedures were done by the same team each time, using the same ruler.

PET test: The patient comes to the hospital 8-12 hours before peritoneal dialysis without emptying the dialysate. In the sitting position, the dialysate is evacuated for 20 minutes and its volume is recorded. With the patient lying supine, 2.27% dialysis solution at a dose of 1100 ml/m^2 is delivered into the peritoneal cavity within 10 minutes. Meanwhile, the patient is turned to his/her right and then left side every 2 minutes to mix the infused solution with the residual dialysate. Immediately after the infusion is completed, 200 ml of dialysate is drained. After a 10 ml sample is taken, the rest is returned to the peritoneal cavity. During the test, the patient walks around. After waiting for 2 hours, 200 ml of dialysate is poured out again and after 10 ml of sample is taken, the remainder is infused into the peritoneum. At the same time 2-3 ml of blood sample is obtained. At the fourth hour, the whole dialysate is emptied in 20 minutes with the patient is in the sitting position. The bag is mixed thoroughly and a final sample of 10 ml is taken. The drainage volume is measured and the sample fluids (30 ml) taken are added to the drainage volume. Creatinine and glucose concentrations in blood and dialysate samples are measured. The ratio between dialysate and plasma creatinine concentrations (D/P creatinine) at the 4th hour of dialysis, and dialysate glucose concentrations between the 4th hour, and beginning of the dialysis (D4/D0 glucose) were calculated.

Peritoneal permeability is considered low if D/P creatinine <0.50, low-medium if 0.50-0.65, high-medium if 0.66-0.81 and highly permeable if >0.81.[10]

Performing the Kt/Vurea test: For the calculation of Kt/V urea, which is the fractional urea clearance standardized according to the urea distribution volume, 24-hour dialysate and 24-hour urine (if not less than 100 ml/day) are collected. After measuring the urea concentrations in blood, dialysate and urine, the Kt/Vurea is calculated using the following formulas.[11]

Dialytic Kt/Vurea= [(D/P urea) x Dialysate discharge volume (L)]/Total body water Renal Kt/Vurea= [(U/P urea) x Urine Volume (L)/Total body water
Weekly total Kt/Vurea=(Dialytic Kt/Vurea + Renal Kt/Vurea) x 7
D: Dialysate urea concentration, P: Plasma urea concentration, U: Urinary urea concentration

Total body water (TBW) was calculated using the Watson formulas:
In males, TBW=(0.3362 x weight) + (0.1074 x height)

+ (0.09516 x age) + 2.447 In females, TBW=(0.2466 x weight) + (0.1069 x height) – 2.097

The parameter of Kt/Vurea was taken as the basis for the dialysis adequacy . Mathematical calculations of Kt/Vurea and PET were made using computer application of "Renal Soft" program.

Statistical Analysis

The analysis of the data was done in SPSS for Windows 15 package program. Shapiro -Wilk test was used to investigate whether the distribution of continuous variables was normal. Descriptive statistics were presented as mean±standard deviation or median (25-75) percentiles for continuous variables, and as number of cases and percentages (%) for categorical variables Whether clinical and laboratory measurements changed significantly over time was examined using the dependent t-test or the Wilcoxon sign test. A significant association (if any) between continuous variables was evaluated with Spearman's correlation analysis. Whether the average change in pressure showed a significant difference according to gender was investigated by Student's t test. The results were considered statistically significant if $p<0.05$.

RESULTS

A total of 16 patients with chronic kidney failure including 9 boys and 7 girls, followed in the CAPD program were included in this study. The mean age of the patients was 14.2±3.7 (7-19) years, and the mean dwell time of dialysis was 54±42 (2-168) months.

Dialysis fill volumes, mean intraperitoneal pressure (IPP), PET and dialysis adequacy parameters of the patients are shown in Table 1.

Mean dialysate volume used for the patients was 1123.4±126.86 ml/m^2 (860-1360 ml/m^2), while the dialysate volume was below 1000 ml/m^2 in 4, and over 1200 ml/m^2 in 3 patients. Mean intraperitoneal pressure was 12.9±2.77 cm/H_2O (8.5-19 cm/H_2O), but it was above 18 cm/H_2O in only one patient. No relationship was found between intraperitoneal pressure and age and sex in the evaluation made considering filling volume ($p=0.187$, $p=0.745$). The mean Kt/Vurea value was 2.5±0.93 (range 1.22 to 4.64). Seven patients had Kt/Vurea values below 2. Four of these patients had no urine output. The mean values and distribution ranges in intraperitoneal pressure, dialysate volume, Kt/Vurea, Uf, Hb, albumin levels of the patients are shown in Table 2.

No relationship was found between intraperitoneal pressure, dialysate volume and dialysis adequacy ($p>0.05$). A statistically significant relationship was found between ultrafiltration and dialysis adequacy

Table 1. Dialysis fill volumes, intraperitoneal pressure and dialysis adequacy parameters of patients

Patients	Duration of dalysis (Month)	PET 1/2*	Volume of dyalisate ml/m^2 1 / 2*	IPP cm/H_2O 1 / 2	Kt/Vur 1 / 2*	Urine volume ml/m^2 day 1 / 2*	UF (ml/day) 1 / 2*	Hemoglobin gr/dl 1 / 2*	Albumin gr/dl 1 / 2*
1.	84	ML/ML	1320/1320	13/17	2.3/2.25	750/500	441/735	7.6 /9.7	3.8/3.89
2.	48	MH/H	1034/1000	10/ 13.5	1.73/1.95	0/0	690/980	8 /10.2	4.1/3.19
3.	60	L/ML	1190/1360	19/ 13.75	1.69/1.75	0/0	675/740	10.6 /6.3	3.8/4.1
4.	36	MH/MH	1000/1000	13/ 14.5	4.55/2.82	2400/2000	1375/425	7/10.7	3.4/3.34
5.	96	H /H	1190/1190	12.5/ 8.5	2.43/2.47	0/0	590/1175	7.9 /11.6	2.9/3.34
6.	24	ML/ML	1200/1170	10.5/10.25	2.41/2.34	300/750	605/450	11.8/11.1	4.8/4.54
7.	72	ML/MH	1150/1000	13.5/11	2.85/1.91	0/0	1150/800	11/7.8	4/3.9
8.	30	MH/H	1300/1100	11.5/12	2.58/2.33	0/0	200/0	8.1/8.3	3.55/3.74
9.	48	H/H	1000/1000	9.75/11.75	3.48/3.0	700/900	500/935	9.3/8.7	2.6/3.0
10.	168	MH/MH	1000/1000	13/13	1.94/1.84	250/300	250/300	9.4/9.1	3.2/3.4
11.	72	H/MH	975/1100	16.5/10.5	1.22/1.79	0/0	125/200	8.5/9.4	3.4/3.1
12.	84	H/(-)	1315/(-)	12.5/(-)	1.23/(-)	0/(-)	260/(-)	6.9/(-)	2.7/(-)
13.	12	H/(-)	860/(-)	11/(-)	3.03/(-)	950/(-)	85/(-)	8.3/(-)	3.4/(-)
14.	1,5	MH/(-)	1078/(-)	12.25/(-)	1.99/(-)	850/(-)	50/(-)	9.4/(-)	2.45/(-)
15.	12	H/(-)	970/(-)	15.25/(-)	4.64/(-)	2500/(-)	0/(-)	10.7/(-)	3.6/(-)
16.	12	ML/ (-)	837/ (-)	12/ (-)	1.83/ (-)	2000/(-)	170/ (-)	10.6/ (-)	3.5/ (-)

** The initial values of the patients and the control values after 6 months were reported as 1/2, respectively.*
H: High, MH: Medium high, ML: Medium low, L: Low, IPP: intraperitoneal pressure, PET: peritoneal equilibration test, Uf: ultrafiltration

Table 2. Dialysate volume, intraperitoneal pressure, dialysis adequacy, ultrafiltration, hemoglobin and albumin levels of the patients

Variables	Mean ± SD
Dialysate volume	1123.4±126.86 (875-1360) ml/m^2
Intraperitoneal pressure	12.9±2.77 (8.5-19) cm/H_2O
Kt/Vurea	2.5±0.93 (1.22-4.64)
Ultrafiltration (ml/day)	600.1±382.15 (-85-1375) ml
Hemoglobin (gr/dl)	9.0±1.54 (6.3-11.8) gr/dl
Albumin (gr/dl)	3.6±0.61 (2.45-4.8) gr/dl

Table 3. PET test results of the patients at baseline and after 6 months

PET test	Beginning n (%)	6th month n (%)
High	6 (37.5%)	3 (%27.2%)
Medium high	5 (31.25%)	5 (%45.6%)
Medium low	4 (25.0%)	3 (%27.2%)
Low	1 (6.25%)	-

(p=0.04). While there was no correlation between intraperitoneal pressure and Kt/Vurea values of dialysate volume used (p=0.670, p=0.121, respectively), a significant change was found between ultrafiltration and Kt/Vurea (p=0.04). No relationship was found between hemoglobin and albumin and dialysis adequacy (p>0.05).

The first and second PET results of the patients who underwent peritoneal dialysis are shown in Table 3.

In the control PET test performed six months later, 8 patients had high and moderate-high, 3 patients had low and moderate-low peritoneal permeability. The second PET test could not be performed in five patients for various reasons. It was found that the peritoneal permeability of one of the patients changed from low to medium-high. The mean dwell times of peritoneal dialysis of the patients with high and moderate-high PET were 62 months, and 36 months for those with low and moderate-low peritoneal permeability. It was found that as the duration of peritoneal dialysis increased, peritoneal permeability was more likely to be high and moderate-high (p=0.04).

Nine of 16 patients had a urine output of 100 ml or more. Kt/Vurea values of 4 patients without urine output were below 2. It was found that the mean duration of dialysis was 44 months for patients with and 66 months for those without urine output. There was no statistically significant relationship between duration of dialysis and urine output (p=0.09).

Dialysate volumes, IPP and dialysis adequacy parameters were evaluated for the second time in 11 patients after 6 months. It was found that there was no change in volume of dialysate used in 5 patients, while it decreased in 3, and increased in other 3 patients (Table 4). When the initial and 6th month dialysis parameters were compared, no statistically significant difference was found between dialysate volumes, IPP, Kt/Vurea, and Uf (p>0.05).

Table 4. The initial and 6th month UF, IPP, dialysis proficiency parameters of the patients

Patients	Initial dialysate volume (ml/m^2)	6th month dialysate volume (ml/m^2)	Initial Intraperitoneal pressure (cm/H_2O)	6th month Intraperitoneal pressure (cm/H_2O)	Initial ultrafiltration	6th month ultrafiltration	Initial Kt/Vur	6th month Kt/Vur
1.	1320	1320	13	17	440	735	2.3	2.3
2.	1035	1000	10	13	690	980	1.73	1.73
3.	1190	1360	19	13.25	675	740	1.69	1.69
4.	1000	1000	13	14.5	1375	425	4.55	4.55
5.	1190	1190	12.5	8.5	590	1175	2.43	2.43
6.	1200	1175	10.5	10.25	605	450	2.41	2.41
7.	1150	1000	13.5	11	1150	800	2.85	2.85
8.	1100	1300	11.5	12	200	0	2.58	2.58
9.	1000	1000	9.75	11.75	500	935	3.48	3.48
10.	1000	1000	13	13	250	300	1.94	1.94
11.	975	1100	16.5	10.5	125	200	1.22	1.22

DISCUSSION

The appropriate dialysis method in children is chosen considering the age, psychosocial status, and the cause of kidney failure.[3] CAPD is the first option in the treatment of CRF due to the technical difficulties of hemodialysis in infants and young children. Peritoneal dialysis fill volume, number of cycles, dialysis fluid content, peritoneal membrane permeability are important factors that determine CAPD adequacy. Therefore, peritoneal dialysis prescriptions should be determined according to the individual parameters of each patient and tried to be optimized.[12,13]

Kt/Vurea is an important criterion in evaluating dialysis adequacy in peritoneal dialysis patients. Although the ideal Kt/Vurea is above 2, it is recommended in the DOQI guideline to keep the weekly total Kt/Vurea value above 1.7, regardless of the peritoneal dialysis method.[14-16] In addition, the definition of dialysis adequacy parameters based on the removal of solutes such as Kt/Vurea is questioned. Although the urea dialysis dose was increased by 30% with this approach, there was no decrease in the morbidity and mortality rates of adult patients using chronic peritoneal dialysis.[17,18] In our study, the Kt/Vurea values of the patients were found to be within normal limits (mean Kt/Vurea. 2.5±0.93). In the initial measurement, Kt/Vurea values of 4 patients were found to be below 1.7. It was observed that by increasing the dialysate volume of two of these patients, the Kt/Vurea values increased above 1.7 in the second measurement without any change in the dialysate volume of the others. There was no change in the Kt/Vurea values of the other patients.

The appropriateness of the peritoneal dialysis fill volume is very important for dialysis adequacy.[19,20] It has been shown that intraperitoneal pressure is an objective criterion reflecting the fill volume. Normal reference ranges for fill volume (1200-1500 ml/m^2), and intraperitoneal pressure (15-18 cm/H_2O) are also specified.[21] Ideal fill volume is 1000-1200 ml/m^2 (7-15 cm/H_2O of intraperitoneal pressure).[21] While low dialysis fill volume causes hyperperfusion, its excessive amount damages the peritoneal membrane and may negatively affect dialysis adequacy. It has been shown that there is an increase of 4 cm/H_2O in intraperitoneal pressure for every 1-liter increase in dialysate volume.[22] In our study, no statistically significant difference was found between the mean fill volume and mean intraperitoneal pressure, and between these parameters and Kt/Vurea. An increase in intraperitoneal pressure above 18 cm/H_2O almost always causes pain.[23] In our study, intraperitoneal pressures were found to be 8.5-19 cm/H_2O at the first measurement. The patient whose fill volume was measured as 1190 ml/m^2 and intraperitoneal pressure as 19 cm/H_2O was found to have no abdominal pain. The intraperitoneal pressure was measured as 13.25 cmH_2O 6 months after the dialysis fill volume of this patient was increased to 1360 ml/m^2 due to dialysis insufficiency. It was found that the intraperitoneal pressure of 3 patients, whose fill volumes were higher than the recommended amount due to insufficient ultrafiltration and dialysis were less than 5 cmH_2O. It has been reported that when the dialysate volume is increased, the intraperitoneal pressure, which is high in the early period, may return to normal over time and the peritoneal membrane will get used to this new condition.[21] In the second evaluation performed 6 months later in our study, it was observed that the intraperitoneal pressure of the patients whose dialysate volumes changed did not change significantly (p=0.247).

Intraperitoneal pressure can be affected by many factors other than dialysate volume such as age, sex, body surface area, body mass index, posture, tolerance acquired over time, constipation, and peritoneal dialysis fluid content. In some studies performed with adults, increased intraperitoneal pressure was found to be associated with complications such as hernia, gastroesophageal reflux, etc.[24], but no complications were detected in our patients. Intraperitoneal pressure is lower in infants compared to adults. Because of higher abdominal tonicity in men, intraperitoneal pressure may be higher.[19,25-28] In our study, no relation was found between intraperitoneal pressure and age or gender of the patients.

In our study, it was determined that the most important factor affecting dialysis adequacy was ultrafiltration. Although the dialysis volume was not increased, an increase was detected in the

ultrafiltration of 3 patients whose intraperitoneal pressures increased. The osmotic pressure difference between the peritoneal capillary blood and the hypertonic dialysate solution creates ultrafiltration, and waste products such as urea and creatinine are removed from the body. Ultrafiltration is one of the important determinants of dialysis adequacy.[21,29] In addition to studies showing that ultrafiltration increases with increasing peritoneal dialysis fill volume,[30-32] there are also studies reporting ultrafiltration was caused by increased lymphatic reflux and therefore decreasing dialysis adequacy. Some of them have reported an increase in mortality and morbidity rates by triggering peritoneal fibrosis in the long term associated with an increase fill volume.[21,33,34] It has been reported that increasing intraperitoneal pressure without an increase in dialysis volume will decrease ultrafiltration and adversely affect dialysis adequacy.[22]

In our study, we found that as the dialysis dwell time increased, PET shifted to the higher side (p=0.04), but ultrafiltration did not decrease (p=0.117). In patients with high permeability, the continuation of ultrafiltration was ensured by switching to instrumental peritoneal dialysis and using dialysis fluid with a higher glucose concentration and isodextrin. The solute transport properties of the peritoneal membrane differ from patient to patient, and this leads to a change in water and solute clearance over time affecting dialysis adequacy. In patients with poor dialysis adequacy parameters, it is recommended to determine a dialysis program while taking into account the peritoneal permeability tests. High permeability of the peritoneal membrane is a poor prognostic indicator.[35] In those with medium-high and high PET values, ultrafiltration also decreases due to the faster loss of the osmotic gradient.

Residual renal function is one of the important parameters that determine the patient's quality of life, and the duration and adequacy of dialysis. However, after starting dialysis, the amount of urine gradually decreases, and if there is an ultrafiltration insufficiency, the volume control of the patient becomes difficult, and the number of antihypertensive drugs used increases. In our study, when the patients were evaluated individually, it was seen that residual renal function was one of the important determinants of dialysis adequacy. The Kt/Vurea values of 9 patients whose daily urine output was 100 ml and above were found to be between 1.9 and 4.6. It was determined that three of the 4 patients with Kt/Vurea values below 1.7 had dialysate volumes of 1000-1365 ml/m^2, and one had a Kt/Vurea value of 975 ml/m^2. All of these patients had no urine output. In 3 patients whose dialysate volumes were below 1000 ml/m^2, but their Kt/Vurea values were above 1.7. It was observed that the daily urine output varied between 950-1000 ml. Statistical evaluation could not be made due to the small number of patients.

With peritoneal dialysis, albumin and protein are lost.[36,37] Albumin level is an important parameter showing dialysis adequacy. In our study, no statistically significant relationship was found between albumin levels and parameters of dialysis adequacy. Like albumin, anemia is an indicator of dialysis adequacy. Anemia may adversely affect hemodynamics in CRF patients and thus impair dialysis adequacy.[36,37] In our study, no statistically significant relationship was found between hemoglobin levels and dialysis adequacy.

Our study, like other studies on this subject, was conducted with a small number of patients. Therefore, some of our results are not compatible with the literature. Another problem is that peritoneal dialysis adequacy is affected by many factors and includes multiple variables.

In conclusion, for adequate peritoneal dialysis, ultrafiltration should be preserved. Therefore, the dialysate volume should be calculated taking into account the intraperitoneal pressure, and dialysis should be prescribed according to the permeability properties of the peritoneal membrane. Further studies with larger case series are required on this subject.

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Case Report

A Newborn Admitted with Hyponatremia and Hyperkalemia Clinic and Diagnosed with Primary Hypoaldosteronism

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ABSTRACT

Primary hypoaldosteronism is a rare autosomal recessive disorder that causes defects in aldosterone synthase enzyme activity due to an inactivating mutation in the CYP11B2 gene. Patients with primary hypoaldosteronism exhibit symptoms such as vomiting, dehydration, feeding problems, and failure to thrive. This disease is characterized by hyponatremia, hyperkalemia, metabolic acidosis, high renin, and low aldosterone levels. It also causes salt loss syndrome in the newborn period. In this article, we described a newborn with primary hypoaldosteronism who showed feeding problems and weight loss. Laboratory findings revealed hyponatremia, hyperkalemia, high plasma renin, and low aldosterone levels, while genetic analysis showed homozygous c.788T>A (p.Ile263Asn) variant in the CYP11B2 gene (NM_000498.3). Our patient responded well to oral salt and fludrocortisone treatments. Early diagnosis and treatment are particularly important because primary hypoaldosteronism causes life-threatening electrolyte disorders and salt loss syndrome.

INTRODUCTION

Aldosterone is a mineralocorticoid hormone that is synthesized only in the zona glomerulosa of the adrenal cortex. By acting on the distal renal tubules and cortical collecting ducts in the kidney, it increases the absorption of sodium and water from the lumen and ensures the excretion of potassium and hydrogen ions into the lumen. The aldosterone synthase enzyme is one of the Cytochrome-P450 enzymes encoded by the CYP11B2 gene, which plays a role in the last three steps of aldosterone biosynthesis. It provides the conversion of 11-deoxycorticosterone (DOC) to corticosterone, the conversion of corticosterone to 18-hydroxy-corticosterone (18-OHB), and finally the synthesis of aldosterone.[1]

Primary hypoaldosteronism occurs because of a defect in the aldosterone synthase enzyme that is developed due to an inactivating mutation in the CYP11B2 gene. It is a rare inherited disorder transmitted as either an autosomal recessive or autosomal dominant trait with mixed penetrance. Its incidence is below 1:1,000,000.[2] There are two types of aldosterone synthase deficiency (ASD) based on the specific defects in aldosterone synthesis: type 1 and type 2. These two types of ASD have similar clinical features. In both conditions, aldosterone cannot be synthesized, and plasma renin activity is elevated. In type 1 ASD, the level of 18-hydroxycorticosterone (18-OHB) is also decreased due to the lack of enzyme activity. On the other hand, in type 2 ASD, the 18-hydroxy-corticosterone (18-OHB) level is increased due to residual enzyme activity.[3] ASD leads to neonatal salt loss syndrome and life-threatening electrolyte imbalances. Clinical symptoms are salt loss, vomiting, dehydration, feeding problems, and developmental delay. It is also characterized by hyponatremia, hyperkalemia, metabolic acidosis, high renin, and low aldosterone levels.[1]

Primary hypoaldosteronism is an exceedingly rare disease. To our knowledge, only 45 cases have been reported in the literature so far.[4] The fact that the clinical course of the disease improves over time may be related to small number of cases. This article presents a case study and a literature discussion about a newborn diagnosed with primary hypoaldosteronism and exhibiting feeding problems and weight loss.

CASE REPORT

Our female patient with a birth weight of 2230 g was delivered normally after 36 weeks of gestation in Cyprus from a primiparous woman. Her parents were Turkish and non-consanguineous. After birth, she was admitted to the intensive care unit because of respiratory distress, which improved after she received oxygen therapy for two days. Feeding problems and weight loss developed on the seventh day.

Upon follow-up, on physical examination her body weight (2100 g), her height (51 cm), her heart rate (165bpm), and her blood pressure were (85/42 mmHg) measured. She had a normal female phenotype without any genital anomaly and skin hyperpigmentation. Laboratory examinations showed that her serum sodium level was significantly low (123 mEq/L: normal range 132-147), while her serum potassium level was significantly high (8.8 mEq/L: normal range 3.6-6.1). Her serum glucose level was within normal limits (92 mg/dl), and there was no metabolic acidosis or alkalosis. Her urine test was normal. Abdominal ultrasonography revealed no abnormality or obstruction in her kidneys or urinary tract.

IV sodium supplementation was started for hyponatremia, and calcium gluconate infusion, sodium bicarbonate infusion, salbutamol nebule, and anti-potassium treatments were started for the treatment of hyperkalemia. Fludrocortisone was started at a dose of 0.05 mg/day, and the dose was gradually increased to 0.2 mg/day due to continued electrolyte disturbances during follow-up. Since her electrolyte imbalance did not improve despite these treatments, she was referred to our hospital at the age of 27 days with a serum sodium level of 135 mEq/L and a serum potassium level of 6.5 mEq/L.

The hormonal tests performed for diagnosis revealed that her plasma renin activity was markedly elevated with >100 ng/ml/h (normal range 2.4-37 ng/ml/h), while her aldosterone level was low with 11.6 ng/dl (normal range 19-141 ng/dl). The results of hormonal tests were as follows: serum adrenocorticotropic hormone (ACTH): 8.2 pg/ml (normal range 0–46), cortisol (9.7 µg/dl (normal range 5.5-22.0), 17-OH-progesterone (17-OHP) 0.37 ng/ml (normal range 0-6.3), and dehydroepiandrosterone sulfate (DHEA-SO_4): 4759 µg/dl.

In terms of salt loss and hyperkalemia, the diagnosis of congenital adrenal hyperplasia was excluded due to normal cortisol and adrenal androgen levels and the lack of virilization findings. The patient with high renin and low aldosterone levels was diagnosed with primary hypoaldosteronism. In the genetic analysis performed to confirm the diagnosis, the homozygous c.788T>A (p.Ile263Asn) variant was detected in the CYP11B2 gene (NM_000498.3). Sequence analysis of the CYP11B2 gene was performed using a next-generation sequencing platform (Illumina MiSeq) with

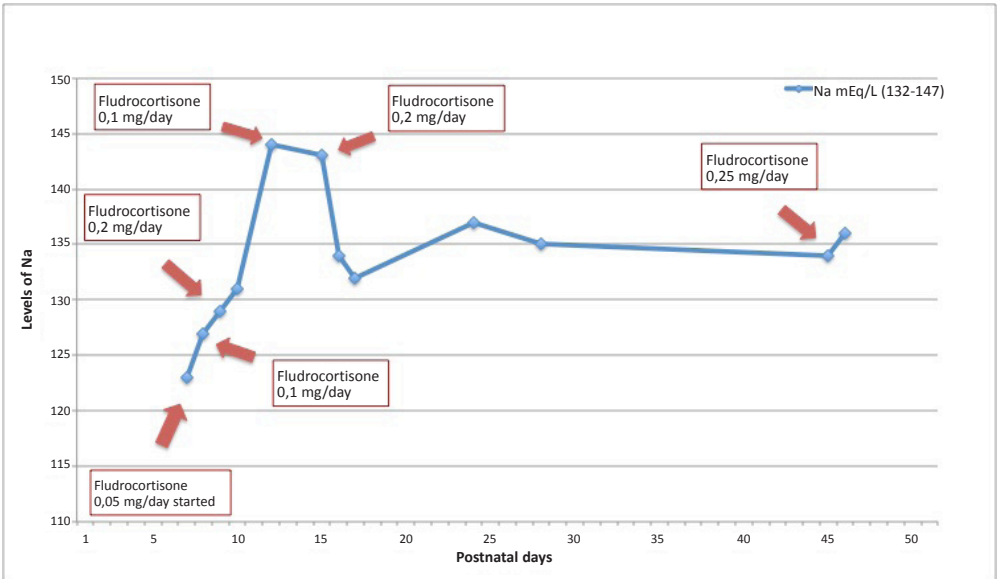

Figure 1. Serum sodium concentrations during the fludrocortisone treatment

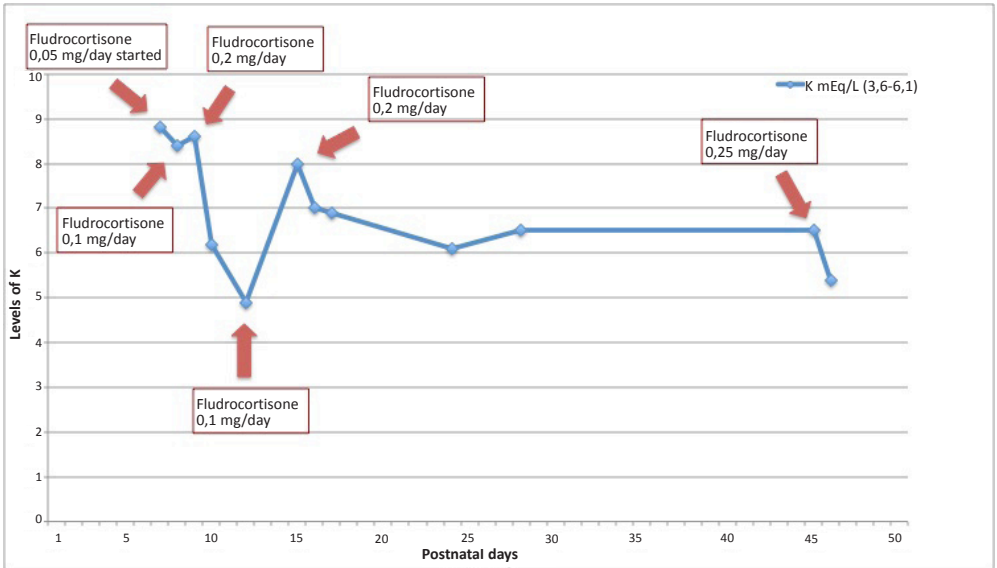

Figure 2. Serum potassium concentrations during the fludrocortisone treatment

PCR-based library preparation. This variant is classified as pathogenic according to the ACMG criteria and its presence in this disease has been previously reported in the literature. The treatment plan of the patient involved daily oral doses of 0.25 mg fludrocortisone and 1 g Na CL supplement. The electrolyte levels returned to normal afterward (Figures 1 and 2).

We continued to follow up our patient in Cyprus, where she received oral doses of 0.1 mg of fludrocortisone and 3 g salt per day. After 15 months, her body weight was 10.5 kg, and her height was 77 cm. The last laboratory tests revealed that her serum sodium level was 137 mEq/L while her serum potassium level was 4.1 mEq/L.

DISCUSSION

In this article, we described a newborn patient with feeding problems and an inability to gain weight.

Hyponatremia, hyperkalemia, high renin, and low aldosterone levels were found, and further genetic testing confirmed that the patient had primary hypoaldosteronism.

Primary hypoaldosteronism typically causes vomiting, signs of dehydration, hypovolemia, and failure to thrive in the first weeks of life. The biochemical assessment revealed hyponatremia, hyperkalemia, increased plasma renin activity, and low aldosterone levels.[4] In rare circumstances, the disease occurs among children and adults with milder phenotypic characteristics. Few cases of normal potassium levels and hyponatremia have been reported in the literature.[5] Our patient exhibited nutritional problems and weight loss on the seventh day. Her serum sodium level was extremely low, and serum potassium level was extremely high, plasma renin activity increased, and aldosterone level decreased. Congenital adrenal hyperplasia (CAH) should be considered in the differential diagnosis of cases with neonatal salt wasting. The presence of genital abnormalities and high adrenal androgen levels guide the diagnosis. In our case, CAH was not considered because there were no signs of virilization and hyperpigmentation. Moreover, cortisol and adrenal androgen levels were all within normal limits. Fludrocortisone treatment was initiated considering primary hypoaldosteronism because of the high renin and low aldosterone levels. Our patient responded well to the fludrocortisone treatment, and improvement was achieved in electrolyte values.

Patients respond well to fludrocortisone therapy, and salt replacement is often needed in the first 1–2 years of life. The recommended starting dose for oral fludrocortisone therapy is 0.1–0.3 mg/day.[3] During follow-up, the patient's dose should be adjusted according to parameters such as blood pressure, serum sodium and potassium levels, and plasma renin activity.[6] The disease is most severe during infancy, and clinical signs improve with age. Adolescents and adults are generally asymptomatic and do not require mineralocorticoid replacement therapy.[4] It is thought that this may be due to the increase in mineralocorticoid receptors and salt intake with age, extra-adrenal compensatory mechanisms, and alternative ACTH-dependent pathways in mineralocorticoid synthesis.[7,8] In our case,oral fludrocortisone treatment was started at 0.05 mg/day and increased up to 0.25 mg/day during follow-up. An oral sodium supplement was added at a daily dose of 1 g. Electrolyte values improved after the treatment.

To our knowledge, only 45 primary hypoaldosteronism cases have been reported so far in the literature. Twenty of these cases were classified as type 1, 12 of them as type 2, and 13 of them were unclassified. In 44 of these cases, symptoms appeared in the first year of life. Growth retardation, recurrent vomiting, and dehydration have been reported to be the most common symptoms. In total, 98% of the cases had hyponatremia, 89% hyperkalemia, 91% elevated PRA levels, and 67% low aldosterone levels. There was no significant difference between type 1 and type 2 cases in terms of clinical findings, biochemical results, and hormone tests except for the 18-hydroxycorticosterone level. Thirty-three (73%) cases received fludrocortisone treatment, and it was reported that symptoms improved in all cases receiving treatment.[4]

In the genetic analysis of our case, a homozygous c.788T> A (p.Ile263Asn) variant was found in the CYP11B2 gene. In the literature, this variant was first reported by Üstyol et al., and Turan et al. detected the same variant in two of three primary hypoaldosteronism cases. To our knowledge, our case is the fourth case of the same ethnic origin but from a different family with the same pathological variant.[5,9] The case reported by Üstyol et al. exhibited salt-wasting like our patient, but unlike ours, the serum potassium level of their case was normal. One of the cases reported by Turan et al. exhibited jaundice and another displayed symptoms like vomiting, growth retardation and dehydration, and hyponatremia and hyperkalemia. We detected the same symptoms in our case. A review of the literature revealed that clinical findings are similar in cases with the p.Ile263Asn and the other variants.[4]

In conclusion, hyponatremia and hyperkalemia are life-threatening electrolyte disorders that require urgent intervention in newborns and infants. A diagnosis of primary hypoaldosteronism should be considered when increased renin levels and relatively low aldosterone levels are detected in patients where congenital adrenal hyperplasia is excluded

from salt loss. In cases diagnosed with primary hypoaldosteronism, clinical and laboratory improvement is achieved with mineralocorticoid and salt replacement therapy.

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Case Report

Diagnostic Approach in Cystinuria: A Case Report

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ABSTRACT

Cystinuria is an, inherited metabolic disorder progressing with recurrent kidney stones due to impaired reabsorption of dibasic amino acids and arises from mutations in the SLC3A1 and SLC7A9 on chromosome 2.
Cystine crystals were detected in the urinalysis of a 17-year-old male patient who was investigated for recurrent kidney stones. Because of demonstration of cystine excretion in the urinary amino acid analysis and having positive family history, we suspected Cystinuria Type B and initiated supportive therapy. However, based on the results of molecular analyses his diagnosis was changed as Cystinuria Type A.
In conclusion, our final diagnosis was changed according to the molecular analyses but our treatment approach did not change. Therefore we would like to emphasize that, prominent physical examination findings and supportive laboratory test results will be sufficient for the diagnosis of cystinuria.

INTRODUCTION

Cystinuria (OMIM 220100) is an inherited metabolic disorder (IMD) caused by a defect in the transport of cystine, lysine, arginine, and ornithine amino acids in the epithelial cells of the small intestine and renal tubular cells.[1] While the worldwide incidence of cystinuria was reported as 1/7000, two different studies from Turkey revealed higher incidences (1/1333 and 1/2065)[2,3] probably due to higher rates (17-22%) of consanguineous marriages in Turkey.[4]

Although reabsorption of cystine, lysine, ornithine, and arginine are all impaired, only cystine excreted in urine causes clinical findings because the other amino acids are soluble. As cystine could not be dissolved well in acidic pH, cystine stones form in the urinary system and cystinuria usually presents with recurrent urinary tract infections and kidney stones in the 2nd or 3rd decade of life. However, there are studies that report nephrolithiasis in infancy due to cystinuria.[5] If the disorder is not treated properly, it may lead to the formation of recurrent kidney stones and development of chronic renal failure in the future.[6] Early diagnosis and treatment prevent these complications. Treatment of cystinuria includes increasing the urinary cystine solubility through hydration, diet modification and urinary alkalinization. As dietary sodium intake increases the excretion of cystine through the urinary tract by an unknown mechanism, the use of sodium bicarbonate is restricted so potassium citrate is used for urinary alkalinization. In cases without any adequate response to this treatment, chelating agents such as D-penicillamine, mercapto propionyl glycine, and captopril are used to convert cystine into more soluble compounds.[7]

The diagnosis of cystinuria can be made easily with noninvasive methods that can be performed in

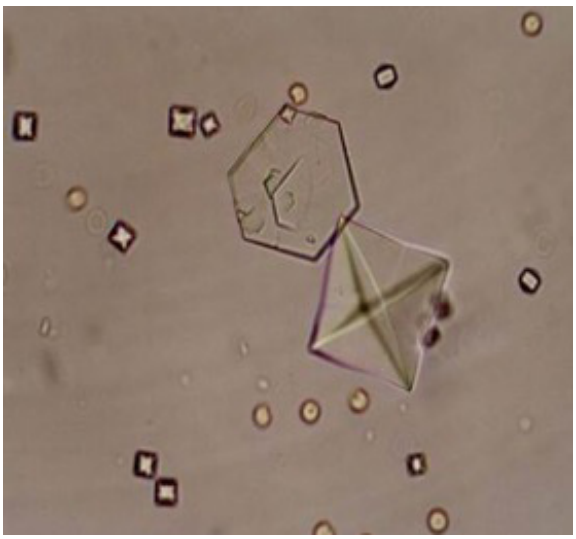

Figure 1. Cystine Crystals on Urine [14]

Figure 2. 1-2 drops of ammonia and 2 ml of 5% sodium cyanide solution added to 5 ml urine. After 5-10 minutes, 5 drops of freshly prepared sodium nitroprusside is added mixed. Changing the colour to red bud indicates the positive reaction.[9]

primary health care services. For definitive diagnosis, observation of cystine crystals on urine microscopy (Figure 1) and demonstration of an increase in cystine excretion in urinary amino acid analysis are considered to be adequate.[6] The observation of cyclamen color change on urine samples with the cyanide-nitroprusside test supports the diagnosis (Figure 2). Stone analysis can also be performed in nephrolithiasis cases. However, it is not necessary for the establishment of the diagnosis, and the treatment can be initiated as soon as possible.[8,9]

As a result of advances in DNA technology, the demonstration of affected genes in the diagnosis of hereditary diseases is one of the leading diagnostic methods used in advanced centers. Sequencing of many genes has shown that each disorder has millions of genetic variants. SLC3A1 or SLC7A9 are the responsible mutations in cystinuria. At least 104 (SLC3A1) and 152 (SLC7A9) different mutations associated with these subtypes have been reported.[5] Some of these variants cause symptomatic disease, some increase the risk of disease occurrence, while others have no clinical effect. Besides, false-negative results can be obtained. However, negative mutation analysis results do not exclude preliminary diagnosis in the presence of obvious physical examination findings and supportive laboratory test results. While it is difficult to assess the exact effects of these mutations, it is still necessary to provide specific treatment options for patients.[1] Therefore, we aimed to discuss whether it is necessary to perform molecular analysis to make the diagnosis of cystinuria.

CASE

A 17-year-old male patient was consulted for investigating the etiology of recurrent urolithiasis. He had no known chronic disease. The constant abdominal pain was started at the age of 10 years, and kidney stones were detected with basic laboratory analyses. Percutaneous nephrolithotomy had been performed twice, but recurrent stone formation continued. Stone analysis revealed a cystine stone. Upon this result, the patient was referred to our clinic.

There was a second-degree consanguineous marriage between his parents. His father and a cousin had also a history of recurrent kidney stones. We couldn't perform their urine amino acids analysis because they were living in different provinces

Physical examination and first step laboratory tests revealed no pathological findings. Stone formation was not observed in direct abdominal radiographs, but more than one echogenicity (calculi?) were

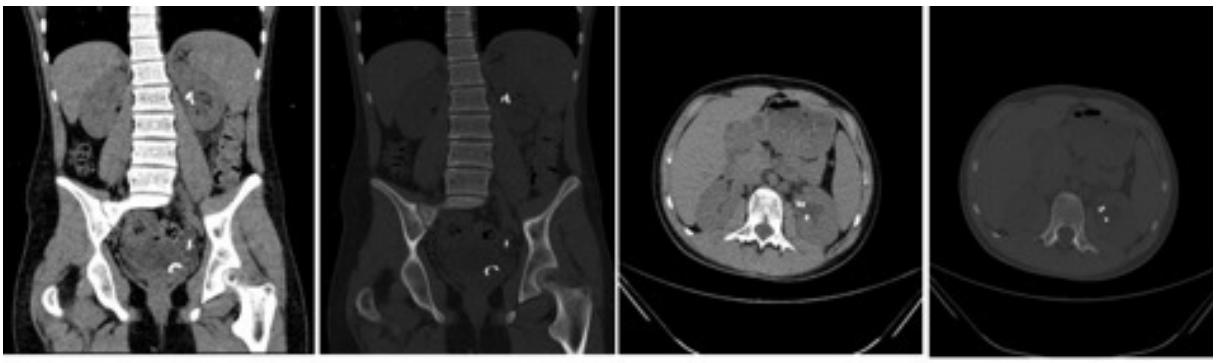

Figure 3. Post-operative cotrol CT images

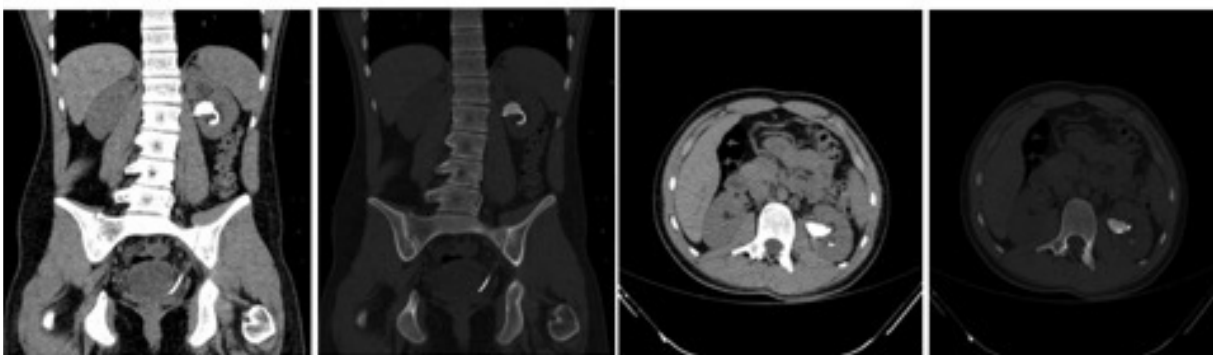

Figure 4. Control CT images after kidney stone recurrence

shown in kidneys by renal ultrasonography. Computed tomography images were also compatible with nephrolithiasis (Figure 3, 4). Upon detection of cystine crystals in microscopic analysis of patient's urine, we planned to perform amino acid analysis in plasma and urine. The cyanide-nitroprusside test was (+++) positive. Analysis of urinary amino acids revealed increased cystine excretion [1675 µmol/gr creatinine (Normal 0-200 µmol/gr creatine)]. With these results, cystinuria was thought and alkalinization of urine with potassium citrate treatment was initiated.

For genetic counseling and family screening we planned to send blood samples for molecular analysis. Primarily, the SLC7A9 gene mutations were evaluated considering autosomal dominant inherited cystinuria (Type B). As the test was negative, Cystinuria Type A was evaluated thereafter. The presence of c.647C> T homozygous mutation in SLC3A1 gene was demonstrated. Although consanguineous marriage indicates cystinuria Type A as the preliminary diagnosis, due to limitation in financial sources we could not send samples of all family members at the same time, priority was given to the children of the family. Genetic counseling was given and family screening was planned, however as some relatives lived abroad they were advised to apply to the nearest metabolic clinic.

For treatment the patient received medications only for urine alkalinization. During the follow-ups, his complaints were resolved, and at the sixth-month visit we observed a significant decrease in urinary excretion of cystine (225 µmol/gr creatinine).

DISCUSSION

Cystinuria is an inherited amino acid transport defect which was first described by Garrod in 1908.[5] The diagnosis is based on showing the excretion of dibasic amino acids in the urine. The observation of hexagonal cystine crystals in urine microscopy is also pathognomonic. While the amount of urinary excretion of cystine in healthy individuals is 50-60 mg/dl/1.73 m^2, this may increase up to 400 mg/dl/1.73 m^2 in cystinuria patients.[10] The maximum cut-off

value is accepted as 150 micromole/mmol creatinine. There would be no change in plasma levels of cystine and other dibasic amino acids. In our case, the amount of urinary cystine excretion was 1675 mg/dl/1.73 m^2 and plasma amino acid concentrations were within normal limits.[11]

Depending on the different mutations, the degree of transport defect of these amino acids varies. Disease is divided into two main clinical subtypes according to these mutations and inheritance type. Cystinuria Type A (Type 1 Cystinuria) is autosomal recessively inherited disease and occurs as a result of a mutation in SLC3A1 gene on the 2nd chromosome, Cystinuria Type B shows an autosomal dominant inheritance and is caused by a mutation in the SLC7A9 gene on the 19th chromosome. In very rare cases, there are two different mutant alleles on the same gene and this rare subtype of cystinuria is defined as Type AB. At the first assessment, we thought that our patient may have Type B cystinuria due to the detection of a high concentration of cystine in the urine and a family history of kidney stones. But molecular analyses revealed no pathological mutation at this gene site. We sent a second sample to detect presumed Type A cystinuria, to be sure of the diagnosis on a molecular basis and a homozygous mutation was found in SLC3A1 gene. In many studies, it has been reported that there is no genotype-phenotype correlation in patients with cystinuria, and also no mutation is shown in 5% of patients.[12,13] Therefore, detection of increased urinary cystine excretion still remains the main tool in assessing the prognosis and deciding on appropriate treatment.

In our case, the existence of consanguinity between parents, a positive family history (father and cousin), positive cyanide nitroprusside test result, increased urinary excretion of cystine, result of the stone analyses and demonstration of stones by imaging techniques have strengthened the diagnosis. As stated above, no mutation might be shown in genetic analysis in some patients. For this reason, physicians should not exclude diagnosis of any inherited disorder in clinical practice based on negative molecular test results.

Cystinuria is the most common cause of kidney stones encountered during childhood.[5] Apart from cystinuria, other metabolic disorders such as hypercalciuria, hyperoxaluria, hypocitraturia, and hyperuricosuria may also cause urolithiasis.[10] Performing molecular analysis in cystinuria cases may also be beneficial in differential diagnosis from other causes of kidney stones. However, it should be kept in mind that, first-line metabolic tests should be the primary step for differential diagnosis.

Diagnosis of cystinuria can be made with a proper anamnesis, an accurate physical examination, and using primary laboratory tests. Genetic tests are not mandatory during diagnostic process. While a positive mutation analysis supports the diagnosis, a negative result does not exclude.

Molecular analysis are expensive methods and are not still available in many clinical centers. The use of this expensive method in the diagnostic process does not provide a significant benefit in the treatment, prognosis or predicting complications of the disease. Therefore examining the cystine crystals in urine and conducting cyanide- nitroprusside test would be enough for accurate diagnosis. Both of these tests could be applied easily and treatment could be initiated without further delay. Subtyping of the disease by molecular analyses in centers with technical capacity would contribute to the scientific literature. Therefore, maintaining a persistent attitude in the presence of clinical suspicion will be useful in the diagnosis of single-gene diseases and in the discovery of new mutations.

CONCLUSION

In recent years, the use of molecular diagnostic methods has increased, especially in inherited metabolic diseases. Due to many diseases caused by unknown genetic mutations or unknown mutations in the relevant gene regions, false-negative results can be obtained by these methods. In the presence of obvious physical findings and supportive laboratory test results as in the presented case, genetic analysis are not needed or negative molecular test results can not exclude the current diagnosis.

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Case Report

Langerhans Cell Histiocytosis with Isolated Central Diabetes Insipidus, Low Grade Fever and Sellar Erosion

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ABSTRACT

Langerhans cell histiocytosis (LCH) is a rare disease of the monocyte-macrophage system. Although it is known that bone involvement is seen very frequently in cases with LCH, our case is the first case with a lytic-destructive lesion in the bone structure forming sella turcica.

A 4-year-old, 5-month-old male patient who applied to our outpatient clinic was diagnosed with Langerhans cell histiocytosis in further examination after the diagnosis of central diabetes insipidus (CDI) was made. On cranial magnetic resonance imaging (MRI), widespread lytic-destructive bone lesions were observed in the bone structure forming the sella (sphenoid bone), sellar destruction not previously described in the literature.

Sellar erosion has not been reported before in cases diagnosed with LCH in the literature. The presence of low-grade fever in a patient presenting with isolated CDI is a warning sign for the diagnosis of LCH.

INTRODUCTION

Langerhans cell histiocytosis (LCH) is a rare clonal disease of the monocyte-macrophage system characterized by uncontrolled proliferation and accumulation of dendritic cells.[1] Its annual incidence rate is estimated as 5 per million for children under the age of 15.[2]

It is diagnosed with clinical and radiological findings together with histopathological analyzes and shows a wide range of clinical findings from self-healing lesions to life-threatening widespread involvement.[1] Unifocal involvement (57%) is the most common form in children diagnosed with LCH, while multisystemic involvement (17%) is less frequent.

Central nervous system involvement is seen in approximately 5% of patients with LCH, and the hypothalamus-pituitary axis (HPA) is most frequently affected as a result of the destruction or degeneration of neurons in the supraoptic and paraventricular nuclei of the hypothalamus.[3]

Our case that was found to have central diabetes insipidus on admission to our clinic with the complaints of polyuria and polydipsia, was diagnosed with multisystem involvement LCH when evaluated with intermittent mild fever. We wanted to present our case so as to share our experiences during the diagnostic process.

CASE REPORT

A 4-year-5-month-old male patient was referred to our outpatient clinic with complaints of drinking too much water and urinating frequently for 2 months. It was learned that he drank 5-6 liters (7-8 L/m^2) of water per day. There was no history of vomiting or weight loss. He did not have a history of chronic disease, continuous medication use, head trauma, or previous infection. On physical examination, his height (103.3 cm: standard deviation score (SDS): 0.89), body weight (17.8 kg; SDS: 0.07), body mass index (16.7 kg/m^2; SDS: 0.74), testicular volüme (2/2 ml), and stretched penile length (4.2 cm) were measured. His pubic hair growth was in stage-1 and prepubertal. Other system examinations were normal except for dry skin. Remarkable laboratory test results were as follows: hemoglobin (Hb): 110 g/L, white blood cell count (WBC): 10.8x10^9/L, platelet (PLT): 602x10^9/L, blood glucose: 4.3 mmol/L, blood-urea-nitrogen: 2.1 mmol/L, creatinine: 41.5 µmol/L, sodium: 141 mmol/L, potassium: 4.65 mmol/L, aspartate aminotransferase: 27 units/L, alanine aminotransferase: 8 units/L, urine density: 1001, and urine pH: 6. The patient was admitted to the pediatric endocrinology service for further examination and treatment with a pre-diagnosis of diabetes insipidus.

After water deprivation test, the patient was diagnosed with diabetes insipidus, and urinary osmolarity increased from 121 mOsm/L to 407.7 mOsm/L after administration of 10 micrograms of desmopressin acetate nasal spray solution (Table 1). With these findings, the patient was diagnosed with central diabetes insipidus (CDI) and desmopressin treatment was initiated. The patient's symptoms of polyuria and polydipsia improved with 3 daily doses of 30 microgram desmopressin acetate (MINIRIN® Melt).

The anterior pituitary functions of the patient were examined (Table 2). A borderline increase in prolactin level, low levels of insulin-like growth factor-1 (IGF-1), slightly lower thyroid-stimulating hormone with normal free thyroxine, adrenocorticotropic hormone

Table 1. Water deprivation test results

Hour (h)	Body Weight (kg)	Loss of Body Weight (%)	Blood Pressure (mmHg)	Heart Rate (bpm)	Serum Sodium (mmol/L)	Serum Osmolarity (mOsm/L)	Urine Osmolarity (mOsm/L)	Urine Density	Urine volume (mL/h)	Plasma ADH (pmol/L)
1st	17		116/56	116	139	284.6	44.7	1001	120	3.69
2nd	16.5	3%	104/66	110	141	288.4	54.4	1001	135	3.96
3rd	16.3	4.2%	116/70	117	144	295	59.2	1001	110	
4th	16.2	4.7%	103/75	125	148	303	121	1004	40	4.78
10 mcg desmopressin was administered intranasally										
5th	16.1	5.3%	105/72	117	145	296.4	245.3	1010	30	
6th	16.1	5.3%	108/72	127	145	296.7	407.7	1016	10	

Table 2. Pituitary functions of the patient with central diabetes insipidus

Tests	Test Results	The Reference Range
TSH (mIU/L)	0.56	(0.6-6.3)
fT4 (pmol/L)	13.5	(11.5-27)
ACTH (ng/L)	< 5	(0-46)
Cortisol (nmol/L)	220.6	(107.5-662)
	Cortisol repetition during stress is 772.4	
IGF-1 (µg/L)	18.3 (<-2 SD)	(50-286)
IGFBP-3 (mg/L)	1.42 (-2/-1 SD)	(1-4.7)
Prolactin (µg/L)	22.06	(2.5-17)

ACTH; Adrenocorticotropic hormone, IGF-1; Insulin-like Growth Factor, IGFBP-3; Insulin-like Growth Factor Binding Protein-3, fT4; Free thyroxine, TSH; Thyroid-stimulating hormone

and cortisol levels were observed. The patient's IGF-1 value was low. When the patient's clinical condition stabilized in the follow-up, it was planned to be examined for growth hormone deficiency. The patient with slightly lower thyroid-stimulating hormone with normal free thyroxine value was considered as euthyroid sick syndrome because of fever observed shortly after the test was performed. Follow-up of thyroid function tests was planned. Cortisol response of the patient during stress was within normal range.

In the follow-up of the patient, it was observed that his body temperature raised to 38-38.4°C in the evening once a day, and fell spontaneously and did not persist. On physical examination, any focus to explain the fever was not found. In laboratory tests, increases in acute phase reactants were observed (WBC: 14.89x10^9/L, PLT:722 x10^9/L, C-reactive protein (CRP): 731.4 nmol/L (0-38), sedimentation rate: 70 mm/h (0-10), ferritin: 81.3 µg/L (6-24), and fibrinogen: 3.96 g/L (1.7-3.5)). No pathogenic microorganism was isolated in the patient's blood or urine culture. Coagulation parameters, liver transaminases and kidney function tests of the patient were within normal limits.

Anemia was found in the laboratory tests performed during febrile episode (Hb: 100 g/L, mean corpuscular volume (MCV): 66.5 fL) and the lungs were clear on chest x-ray. The patient with CDI and fever was consulted to the oncology department for the pre-diagnosis of LCH. A lytic expansile bone lesion in the mid-diaphyseal part of the left clavicle was found on

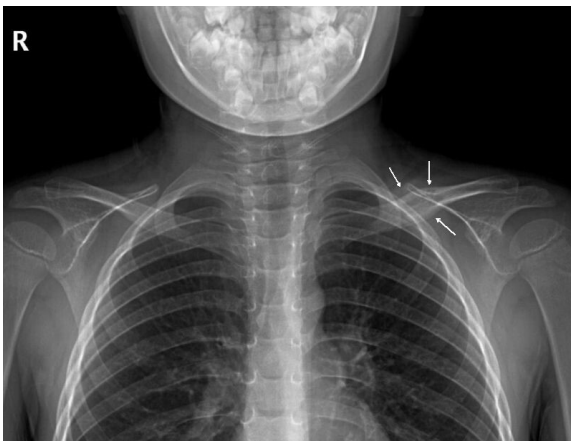

Figure 1. Skeletal survey of the patient shows a lytic expansile bone lesion in the mid- diaphyseal part of the left clavicle (white arrows)

skeletal survey (Figure 1). In the thorax computed tomography (CT) of the patient, a mass lesion with mild expansion, cortical thickening and cortical destruction was observed in the left clavicle mid-diaphyseal section. Lung parenchyma and other findings were unremarkable.

On magnetic resonance imaging (MRI) of the patient's pituitary gland, the height of the anterior pituitary gland was measured as 8 mm which was slightly increased according to the patient's age. The infundibulum was significantly thick and the transverse diameter was measured 6 mm. The bright signal of the neurohypophysis was not observed in the T1-weighted image. In addition, heterogeneous-nodular-mass-like enhancement was observed in the adenohypophysis and infundibulum after intravenous

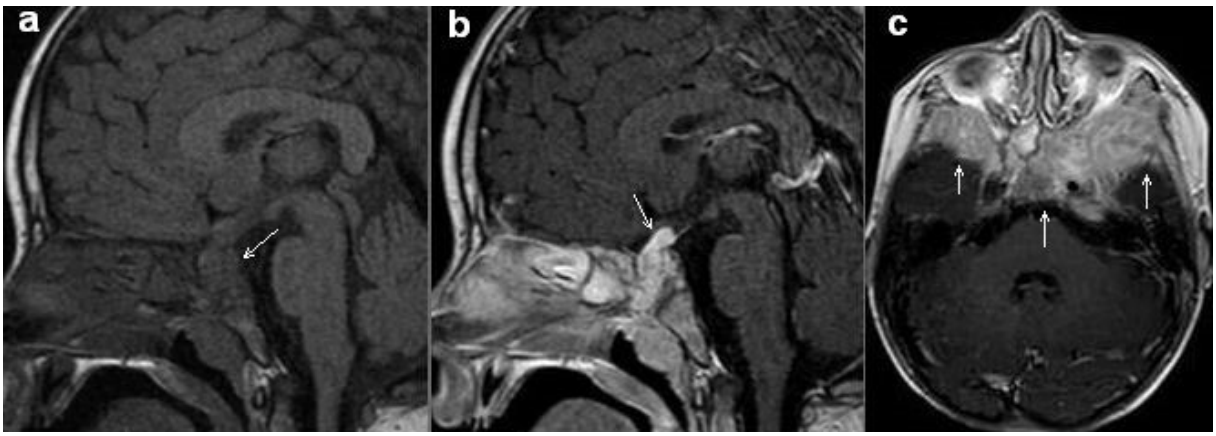

Figure 2 (a-c). Sagittal plane T1-weighted MR image (a) reveals the absence of posterior pituitary bright spot (white arrow). Note the destruction of sella turcica and the body of the sphenoid bone. Sagittal plane post-contrast T1-weighted MRI (b) demonstrates the thickened, and contrast-enhanced pituitary stalk (white arrow). Also, note the heterogeneous enhancement of the sphenoid bone around the pituitary gland. Axial plane post-contrast T1-weighted MRI of the brain (c) shows the destruction and infiltration of the skull base, more prominently on the sphenoid bone which is enhancing heterogeneously (white arrows)

contrast agent (IVCA) injection. On cranial MRI, widespread lytic-destructive bone lesions were observed in the bone structure forming the sella turcica, and the lateral wall of the left orbita. Also, intensely heterogeneous enhancement in the bone marrow was observed after IVCA injection (Figure 2). Because of the marked thickening in the infundibulum, serum alpha-fetoprotein and human chorionic gonadotropin levels of the patient were determined for the differential diagnosis of dysgerminoma. It was observed that the results were within normal ranges. The patient, who had a pre-diagnosis of LCH, was directed to an external center for bone biopsy and it was learned that the treatment for the diagnosis of LCH was planned.

DISCUSSION

Central diabetes insipidus is a disease characterized by polyuria and polydipsia due to arginine vasopressin deficiency as a result of the destruction or degeneration of neurons originating from the supraoptic and paraventricular nuclei of the hypothalamus. Although 30-50% of the cases are idiopathic, known causes include intracranial tumors such as germinoma, craniopharyngioma, Langerhans' cell histiocytosis, granulomatous causes such as sarcoidosis, tuberculosis, hypoxic/ischemic vascular diseases, autoimmune diseases, trauma caused by central nervous system surgery or injury, and genetic defects that affect vasopressin synthesis.[4] An organic cause should be investigated in children diagnosed with CDI. Various other diseases, especially germinomas, should be excluded.[1] In a series of 34 children with CDI, it was reported that four patients (7%) had LHH in etiology.[5] Central diabetes insipidus is the distinctive finding of HPA infiltration in cases with LCH. It occurs in 25% of all patients with LCH or up to 50% of patients with multisystem disease.[1] The frequency of isolated CDI has been reported to be less than 2 in 13 million per year in individuals younger than 18 years of age.[6] In approximately 50% of cases with CDI, deficiency of anterior pituitary hormones also develops and causes growth retardation, hypothyroidism, hyperprolactinemia, hypoadrenalism, hypogonadism, amenorrhea, precocious puberty or delayed puberty.[3]

In our case, the presence of febrile episode that occurs once in the evening and falls off spontaneously led to the exclusion of infectious causes, but no pathological finding was found in the lung radiogram. Cases with LCH may sometimes present with fever and the importance of this finding is not clearly known. Tetsuko et al. analyzed 40 LCH cases retrospectively in their study and reported that 25% had persistent fever at the beginning (>38°C). They stated that cases with LCH who had fever at the time of diagnosis and had higher WBC, soluble interleukin-2 receptor and CRP values, lower Hb

and MCV values indicated the presence of more intractable disease pattern. When the patterns of the febrile episodes of the patients were evaluated in the study, it was reported that periodic fever was observed in 2, persistent fever in 4, and intermittent fever in 2 patients.[7] The fever of our case showed an intermittent course.

In the pituitary gland MRI of our case, it was observed that the height of the pituitary anterior gland was measured as 8 mm and increased slightly with age, the infundibulum was significantly thick and the transverse diameter was measured as 6 mm, and the bright signal of the neurohypophysis was not observed in the T1-weighted image. Varan et al. evaluated pituitary imaging findings in 13 patients with Langerhans cell histiocytosis (LCH) and diabetes insipidus. The infundibulum was thickened in 11 (84.6%), thread-like in 1 (7.7%), and normal in 1 (7.7%) patient. Posterior pituitary intensity was absent in 10 patients (76.9%). In 4 patients, the pituitary gland was small in size, and 2 patients had atrophic pituitary. Three patients had a small sella. Infundibular thickening and absence of posterior pituitary intensity were the most common radiological findings.[8]

In the brain MRI findings of our case, diffuse lytic-destructive bone lesions were observed in the bony structure forming the sella, the sphenoid bone, and the left orbital lateral wall (Figure 2). Approximately 50% of cranial MRIs of patients with LCH have lesions in the craniofacial bones.[1] In a study Lau et al. demonstrated that 50% of the cases with LCH had skull involvement which was significantly more frequently seen in cases with multiple system involvement compared to those with single system involvement (76% versus 42%).[9] Lytic lesions of the skull bones are very common and these lesions may cause abrasions in the dura, but do not progress to the cortex.[1]

In our case, considering the diagnosis of LCH in presentation with isolated CDI, the presence of low-grade fever with intermittent character emphasized that it is a warning sign for the diagnosis of LCH. But the patients with CDI should be evaluated in terms of LHH, the most known underlying cause, regardless of the presence of fever.

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