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RESEARCH ARTICLE

Near-Infrared Spectroscopy (NIRS) Monitoring in Pediatric Shock, and The Effect of Fluid Resuscitation on Multisite NIRS Values

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ABSTRACT

Objective: To study the effects of fluid resuscitation on cerebral (cSO_2) and renal tissue oxygenation (cSO_2) in pediatric shock patients.
Methods: Prospective, observational study in a tertiary PICU (January- September 2016). We monitored bilateral cSO_2 and rSO_2 via NIRS during fluid resuscitation.
Results: Twenty-five patients (56% female) with compensated shock were included. Median age was 19 months (IQR 10-85). Median weight was 12 kg (IQR 5.9-20). The mean left and right brain tissue oxygenation (cSO_2) of the patients participating was 57.7±16.4 and 54.1±16.7, mean left and right kidney tissue oxygenation (rSO_2) was 63.1±14.1, and 62.8±14.8. Tissue oxygen saturation increased significantly after fluid resuscitation The decline in lactate level and the increase in systolic and diastolic blood pressures was statistically significant. The median absolute differences between R-L cSO_2 and rSO_2 at time 0 were 5 (IQR 4-7), and 4 (IQR 1-9) respectively, but the difference was significant only for the brain (p=0.046). Bilateral cSO_2 and rSO_2 increased significantly after fluid bolus in survivors, whereas in non-survivors (n=9, 36%), there was no significant change. The mortality scores of the non survivors were higher than survivors (p<0.005).
Conclusions: This study provides insights into laterality and pediatric cerebral and renal NIRS measurements in critically ill children and may facilitate the interpretation of NIRS data in critically ill patients. Further research with a larger cohort of healthy and critically ill patients is needed to confirm these findings.

Keywords: Near infrared spectroscopy, shock, tissue oxygen saturation, fluid resuscitation

INTRODUCTION

Shock is a critical medical condition characterized by severe disruption of the circulatory system, where tissues cannot meet their oxygen and other nutrient needs. A unifying factor among all types of shock is disruption of cellular metabolism and energy production, which ultimately result in reduced blood flow to vital organs (1). In the initial phase of shock, blood flow to critical organs like the brain, heart, and kidneys is preserved by reducing blood flow to the skin, muscles, stomach, and intestines. This adjustment helps maintain cardiac output at a nearly normal level, thereby preventing the development of hypotension (2). In children, systemic vascular resistance and vasoactive capacity are elevated to prevent rapid and easy decreases in blood pressure. Consequently, hypotension in children is a late indicator of shock that can complicate early diagnosis (3). The objective of shock treatment is to enhance oxygen delivery to tissues. In the event of failure of compensation mechanisms during a state of shock, hypoxia in tissues will worsen, resulting in the development of multiple organ failure and ultimately leading to death. Implementing early recognition and intervention strategies in the context of shock can potentially enhance prognosis (4-5). It has been demonstrated that the parameters used during standard monitoring, including peak heart rate, mean arterial pressure, and arterial oxygen saturation, are insufficient for the detection of early-stage tissue oxygenation. Clinical examinations and laboratory tests (base deficit, lactate) only reveal perfusion abnormalities after a certain period has elapsed. However, there is a lack of complete coherence between macro- and microcirculation in shock (6-7-8-9). In order to address this monitoring gap, studies have introduced the evaluation of tissue oxygenation using near-infrared spectroscopy (NIRS).

The NIRS method can continuously and noninvasively assess tissue oxygenation and indirectly assess hemodynamics

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by measuring changes in oxy-deoxyhemoglobin (ODH) concentrations in the blood. The NIRS value should accurately reflect the mixed venous saturation (~20% arterial, ~5% capillary, and ~75% venous blood) (10). In pediatric patients, NIRS is a commonly preferred method for monitoring tissue oxygenation status, particularly before cardiac surgery, during cardiopulmonary bypass, and in intensive care units. In general, it is expected that healthy children and adults have NIRS values between 60 and 80 per the cent. Cerebral perfusion may be 5%–20% lower than that of somatic perfusion because of higher oxygen extraction in the brain. Clinical data from both children and adults suggest that cerebral cSO_2 levels 40 % to 50% or a reduction of >20% from baseline, are linked to hypoxic-ischemic neural injury (11-12-13). The manufacturer recommends monitoring regional saturation on both sides, although clinical studies almost exclusively report data collected from one side only. The non-invasive nature of the NIRS method, the portability of the devices used, and their ability to provide immediate, cost-effective, and continuous tissue perfusion parameters without the need for invasive procedures have made it a frequent choice in clinical research and patient monitoring. NIRS offers a non-invasive, continuous, and approximate insight into regional oxygenation based on physiological principles. However, the most optimal approach is to base decisions on the analysis of trends exhibited in the graphs over time instead of relying exclusively on the assessment of instantaneous values (14).

The current study aimed to assess the effects of fluid resuscitation on cerebral and renal tissue oxygenation via double-sided (bilateral) NIRS monitoring along with hemodynamic and laboratory parameters (lactate and base deficit) in pediatric patients with shock.

MATERIALS AND METHODS

This was a prospective, observational study with institutional ethics approval (09.2016186) and intramural grant support (BAPKO SAG-C-TUP-131216-0524). The study included 25 patients aged between 1 month and 18 years who required fluid resuscitation support due to compensated shock, from January 2016 to September 2016, at a tertiary Pediatric Intensive Care Unit. Patients with decompensated shock who were receiving inotrope and those with a wound dressing on which the NIRS probe was to make contact were excluded from the study. We compared the vital signs, blood gas parameters, mortality scores, and cerebral and renal NIRS before and after fluid resuscitation. During fluid bolus administration, the INVOS 5100 C Cerebral/Somatic Oximeter (Medtronic) device, which is routinely used in our unit, was used. Demographic and clinical characteristics of the patients, NIRS data (brain-kidney), fluid bolus duration, mortality scoring, and routine laboratory data (blood gas, blood count, biochemical values) were recorded. Two NIRS probes were placed on the frontal region of the patient in a state of shock, and two probes were placed on the T10-L2 kidney level. Patients received a bolus of crystalloid solution at a dose of at least 20 cc/kg within 15-20 minutes. In the event of continued clinical indications for fluid boluses (i.e., prolonged capillary refill, weakened peripheral pulses, tachycardia), repeated boluses were administered.

All hemodynamic parameters and NIRS values were recorded in the central system developed and made ready for use in the project "Centralization of Alarms in the Pediatric Intensive Care Unit and Examination of Smart Alarm Algorithms (Scientific Research Projects Unit Commission, Project No: SAG-A-100713-0297)". The system automatically transferred all relevant data, as measured from the patient monitor, NIRS screen, and ventilator (if connected), to a desktop computer in Excel file format. Measurements were also manually recorded at 5-min intervals.

Frequency tables (n.%) were used for categorical variables, and descriptive statistics (mean, median, standard deviation, etc.) were used for numerical variables. If numerical variables were not distributed normally, analyses were performed using non-parametric statistical methods. The Mann–Whitney U test was used for group comparisons between the two groups. Before-after comparisons were performed using the Wilcoxon test. The threshold of statistical significance was taken as $p<0.05$. SPSS 21 software was used for the analyses.

RESULTS

Twenty-five patients with compensated shock (56% female) were included. Median age was 19 months (IQR 10-85). Median weight was 12 kg (IQR 5.9-20). Most patients had comorbidities (84%). Comorbidities included oncologic malignancies (n=8), severe neurologic problems (n=7), hemolytic anemia (n=1), combined immune deficiency (n=1), mitochondrial disease (n=1), achondroplasia (n=1), prune belly syndrome (n=1), and anal and esophageal atresia (n=1). Shock occurred due to hypovolemia (72%) and sepsis (28%). Fluid bolus was initiated on the basis of clinical criteria of inadequate perfusion based on tachycardia, prolonged capillary refill, diminished pulses, and changes in mental status. Four patients required a second fluid bolus.

The mean left and right brain tissue oxygenation (cSO_2) of the patients participating in the study was 57.7±16.4 and

Table 1. Tissue oxygenation before and after fluid resuscitation

		Mean (SD)	Median (IQR)	Min-Max	p
cSO_2 (L)	**Before**	57.7±16.4	58 (47.5-72)	24-92	0.027*
	After	62.6±18	65 (51.5-71.5)	15-91	
cSO_2 (R)	**Before**	54.1±16.7	55 (44-65)	16-95	0.004*
	After	58.6±17.2	58 (44.5-72.5)	15-95	
rSO_2 (L)	**Before**	63.1±14.1	61 (50-74)	43-91	0.004*
	After	69.4±19.3	73 (57-84.5)	15-95	
rSO_2 (R)	**Before**	62.8±14.8	62 (51-74.5)	31-95	0.010*
	After	69.4±18	71 (57.5-86.5)	15-93	

cSO_2 (L): left cerebral oxygen saturation, cSO_2 (R): right cerebral oxygen saturation; rSO_2 (L): left renal oxygen saturation, rSO_2 (R): right renal oxygen saturation

54.1±16.7, mean left and right kidney tissue oxygenation (rSO_2) was 63.1±14.1, and 62.8±14.8. The median absolute differences between R-L cSO_2 and rSO_2 at time 0 were 5 (IQR 4-7), and 4 (IQR 1-9) respectively, but the difference was significant only for the brain (p = 0.046). Renal tissue oxygen saturation was higher than brain oxygen saturation in 64% (n=16) of patients. Tissue oxygen saturation increased significantly after fluid resuscitation (Table 1), but the absolute difference between the right and left cSO_2 and rSO_2 remained unchanged (p=0.94, p=0.84). The mean cSO_2 and rSO_2 of survivors trended higher than those of non-survivors before the fluid bolus, but the difference was not significant (p>0.05).

The decline in lactate levels and the increase in systolic and diastolic blood pressures were statistically significant after the bolus. There were no significant differences in base excess, respiratory rate, SpO_2, and heart rate before and after resuscitation (Table 2). Bilateral cSO_2 and rSO_2increased significantly after fluid bolus in survivors, whereas in nonsurvivors (n:9, 36%), there was no significant change (Table 3A-3B). The mortality scores of non-survivors were higher than survivors (p<0.005).

Table 2. Vital and blood gas levels before and after fluid resuscitation

		n	Mean±Std Dev.	Median	Min-Max	p
SpO_2	**Before**	25	95,1±7,7	98	66-100	0,147
	After	25	93,2±19,9	99	0-100	
HR	**Before**	25	142,8±40,1	152	56-203	0,078
	After	25	137,8±33,9	139	71-197	
SBP	**Before**	25	84,4±23,3	85	45-136	0,001*
	After	25	97,4±19,8	94	68-139	
DBP	**Before**	25	45,8±21,5	49	13-96	0,004*
	After	25	55,4±15,6	55	25-96	
BE	**Before**	25	-4,03±6,91	-1,8	-18,6-6,7	0,809
	After	25	-3,32±5,95	-3,6	-13,8-9,1	
Lactate	**Before**	25	3,38±2,4	2,7	0,6-8,7	0,009*
	After	25	2,29±1,65	1,6	0,7-7,4	
RR	**Before**	25	37,3±16,2	32	12-77	0,893
	After	25	36,8±14,3	35	15-63	

SpO_2: pulse oximetry, HR: heart Rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, BE: baz excess RR: respiratory rate

Table 3A. Tissue oxygenation values before and after fluid resuscitation in survivors

	Survivors	n	Mean±Std Dev	Median	Min-Max	p
cSO_2 (L)	**Before**	16	62±16,5	66	28-92	0,024*
	After	16	69,3±13,3	69,5	44-91	
cSO_2 (R)	**Before**	16	59,5±14,3	61	34-95	0,013*
	After	16	65,1±14,2	65,5	43-95	
rSO_2 (L)	**Before**	16	65,1±15	62	43-91	0,003*
	After	16	73±15,3	75,5	45-95	
rSO_2 (R)	**Before**	16	63,5±17	62	31-95	0,008*
	After	16	73,2±14,1	73,5	51-92	

cSO_2 (L): left cerebral oxygen saturation, cSO_2 (R): right cerebral oxygen saturation; rSO_2 (L): left renal oxygen saturation, rSO_2 (R): right renal oxygen saturation

Table 3B. Tissue oxygenation values before and after fluid resuscitation in non-surviving patients

	Non-survivors	n	Mean±Std Dev	Median	Min-Max	p
cSO_2 (L)	**Before**	9	50±14	48	24-73	0,575
	After	9	50,7±19,9	54	15-75	
cSO_2 (R)	**Before**	9	44,4±16,9	44	16-70	0,435
	After	9	47,1±16,7	45	15-71	
rSO_2 (L)	**Before**	9	59,6±12,4	57	44-83	0,4
	After	9	63±24,7	59	15-95	
rSO_2 (R)	**Before**	9	61,7±10,9	58	48-75	0,4
	After	9	62,6±22,8	61	15-93	

cSO_2 (L): left cerebral oxygen saturation, cSO_2 (R): right cerebral oxygen saturation; rSO_2 (L): left renal oxygen saturation, rSO_2 (R): right renal oxygen saturation

DISCUSSION

Shock is a leading cause of mortality and morbidity in children. Time is critical in shock management because early diagnosis and targeted treatment significantly reduce mortality and morbidity rates. Currently, there are no specific or sensitive methods to aid in the early recognition of sepsis. To address this gap, previous studies have explored the use of NIRS to evaluate tissue oxygenation. Recognizing that trends and changes in tissue oxygenation are more significant than the absolute values. A reduction in the NIRS value indicates impaired tissue perfusion. In our study, the mean left and right brain tissue oxygenation (cSO_2) of the patients participating in the study was 57.7±16.4 and 54.1±16.7, mean left and right kidney tissue oxygenation (rSO_2) was 63.1±14.1, and 62.8±14.8. Bilateral cerebral and renal perfusion increased significantly after fluid resuscitation. The kidney tissue saturation values of 64% of patients were higher than the brain saturation values, which is consistent with the findings of previous research in this area. In the literature, Hanson et al. demonstrated that brain perfusion was preserved in children presenting with acute dehydration, whereas renal perfusion increased following fluid resuscitation in the emergency department (15). In an animal study, piglets were experimentally placed in hypovolemic shock. They observed that cerebral and renal perfusion increased significantly after resuscitation (16).

Blood lactate level is a biochemical marker frequently used to evaluate tissue hypoxia resulting from compromised oxygen delivery or use during shock management. In our study, the decline in lactate levels and the increase in systolic and diastolic blood

pressures after fluid resuscitation were statistically significant. In a similar study, Tayar et al. identified a significant negative correlation between cerebral tissue perfusion and lactic acid as well as a positive correlation with mean arterial pressure (17).

A study investigating the effect of cerebral perfusion on predicting prognosis in shock patients found a significant difference in regional cerebral oxygen saturation between survivors and non-survivors after 72 hours in the intensive care unit. (52.58% ± 7.33% and 44.75% ± 9.44% (p=0.049) (17). Balakrishnan et al. reported that children with cerebral tissue oxygen saturation <70% in the first 4 hours after arrival to the pediatric intensive care unit had significantly higher PRISM 3 and PELOD scores compared to NIRS>70% (18). Alexandre et al. found SOFA and APACHE II scores were significantly higher in adult patients admitted to the intensive care unit with baseline tissue oxygen saturation below 70% who continued low saturation after resuscitation (19). Vorwerk and Coates found that a persistent low StO_2 (muscle tissue oxygenation) level (below 75%) following resuscitation in patients with septic shock had a double risk of mortality (RR 2.1%, 95% CI 1.2% to 3.5%; p=0.008) (20). In our study, the mortality scores of the surviving patients were significantly lower than those of the non-surviving patients. The mean cerebral and renal oxygen saturation values of the surviving patients were higher than those of the non-surviving patients, but the differences were not statistically significant due to the limited number of patients.

In the literature, because it is easier to collect data, many NIRS studies of patients in shock tend to use the thenar muscle. There are only a few studies using bilateral measurements. However, these have primarily been used to assess brain tissue oxygen saturation in pediatric cardiovascular and interventional cardiology. Although typically used unilaterally, studies have shown that localized neuronal activation can cause regional changes in cerebral blood flow and oxygenation (21-22-23). There is currently a lack of clarity regarding the difference in right-left brain and kidney tissue oxygen saturation in both healthy and shock persons. Although there are not many studies, it is generally accepted in pediatric cardiac practice that the difference between hemispheres is 5-10% at stable systemic oxygenation. Lemmers et al. demonstrated a strong correlation between the oxygenation values of the right and left cerebral tissues in a cohort of 36 very-low-birth-weight preterm infants (r=0,89; p < 0.01). Furthermore, premature infants with unstable arterial saturation may demonstrate discrepancies between the right and left sides (24). Kussman et al. reported that bihemispheric measurements were similar during pediatric cardiac surgery (≤2 percentage points/ absolute scale units) (25). The present study included 12 patients with a right-left brain difference of more than 10%. Five patients died during the follow-up period. There were 9 patients with a right-left kidney difference of >10% and 4 of them died during follow-up. Our study is the only one to use NIRS to evaluate four regions (right-left brain, kidney) in children in shock with short-term recordings in the pediatric age group.

The discrepancy between right and left differences among patients may not be solely attributable to saturation (SpO_2). Regional blood flow, false-positive measurements, and intra- and inter-patient variation can also contribute to the observed differences between the right and left sides. The presence of right-left differences indicates that unilateral measurements may not be sufficient for patient monitoring. Further studies with larger numbers of patients are necessary for evaluating the left-right difference as a prognostic factor.

It is noteworthy that in healthy children without shock, no significant difference was observed between the right and left sides. In our previous study, we demonstrated no discernible differences in cerebral and renal NIRS values between the right and left sides in healthy children (26). The findings of our study support the notion that multisite NIRS monitoring could have prognostic importance in critically ill pediatric patients. However, further studies are needed to define the differences between the right and left sides.

This study has several limitations. The sample size of 25 was relatively small. Moreover, the positioning of renal probes was based on anatomical landmarks without the use of ultrasound scans to verify the position. Despite its limitations, this study provides insights into laterality and pediatric cerebral and renal NIRS measurements in critically ill children and may facilitate the interpretation of NIRS data in critically ill patients. Further research with a larger cohort of healthy and critically ill patients is needed to confirm these findings.

Ethics Committee Approval: This study was approved by the ethics committee of Marmara University (09.2016186) and intramural grant support (BAPKO SAG-C-TUP-131216-0524).

Informed Consent: Written consent was obtained from the participants.

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Author Contributions: Conception/Design of Study- B.A., N.Y.Ö.; Data Acquisition- B.A.; Data Analysis/Interpretation- B.A., F.G.İ., E.U., N.Y.Ö.; Drafting Manuscript- B.A., N.Y.Ö.; Critical Revision of Manuscript- B.A., F.G.İ., E.U., N.Y.Ö.; Final Approval and Accountability- B.A., F.G.İ., E.U., N.Y.Ö.

Conflict of Interest: Authors declared no conflict of interest.

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REFERENCES

1. Brierley, J., Carcillo, J. A., Choong, K., Cornell, T., DeCaen, A., Deymann, A. et. al. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. Crit Care Med. 2009 Feb;37(2):666-88.
2. Sinha, R., Nadel, S., Kissoon, N., Ranjit, S., Shaffner DH, Nichols DG. Recognition, and initial management of shock. Rogers' Textbook of Pediatric Intensive Care. 2016th ed. Wolters Kluwer, 2016, 380-92.

3. Hilarius, K.W.; Skippen, P.W.; Kissoon, N. Early recognition and emergency treatment of sepsis and septic shock in children. Pediatr Emerg Care. 2020 Feb;36(2):101-106.
4. Davis, A. L., Carcillo, J. A., Aneja, R. K., Deymann, A. J., Lin, J. C., Nguyen, T. C. et. al. American College of Critical Care Medicine clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock. Crit Care Med. 2017 Jun;45(6):1061-1093.
5. Rivers, E., Nguyen, B., Havstad, S., Ressler, J., Muzzin, A., Knoblich, B. et. al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001 Nov 8;345(19):1368-77.
6. Ince, C. Hemodynamic coherence and the rationale for monitoring the microcirculation. Crit Care. 2015;19 Suppl 3(Suppl 3): S8.
7. Arteaga, G.M. and Crow, S. End organ perfusion and pediatric microcirculation assessment. Front Pediatr. 2023 Sep 29:11:1123405.
8. Huber, W., Zanner, R., Schneider, G., Schmid R, Lahmer T. Assessment of regional perfusion and organ function: less and non-invasive techniques. Front Med (Lausanne). 2019:6:50.
9. Hariri, G., Joffre, J., Leblanc, G., Bonsey, M., Lavillegrand, J. R., Urbina, et. al. Narrative review: clinical assessment of peripheral tissue perfusion in septic shock. Ann Intensive Care. 2019; 9:37.
10. Donnelly, P., & Fine-Goulden, M. R. How to use near-infrared spectroscopy. Arch Dis Child Educ Pract Ed. 2020 Feb;105(1):58-63.
11. Hoffman, G.M.; Ghanayem, N.S.; Tweddell, J. S. Noninvasive assessment of cardiac output. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu. 2005:12-21
12. Levy, W. J., Levin S, Chance B. Near-infrared measurement of cerebral oxygenation: correlation with electroencephalographic ischemia during ventricular fibrillation. Anesthesiology. 1995 Oct;83(4):738-46.
13. Austin III, E. H., Edmonds Jr, H. L., Auden, S. M., Seremet, V., Niznik, G., Sehic, A. et. al. Benefit of neurophysiologic monitoring for pediatric cardiac surgery. J Thorac Cardiovasc Surg. 1997 Nov;114(5):707-15, 717; discussion 715-6.
14. Chakravarti, S., Srivastava S, Mittnacht AJ. A.J. Near-infrared spectroscopy (NIRS) in children. Semin Cardiothorac Vasc Anesth. 2008 Mar;12(1):70-9
15. Hanson, S.J.; Berens, R.J.; Havens, P.L.; Kim, M.K.; Hoffman, G. M. Pediatr Emerg Care. 2009 Mar;25(3):150-3.
16. Borg, U., Katilius JZ, Addison PS. Near-Infrared Spectroscopy Monitoring to Detect Changes in Cerebral and Renal Perfusion During Hypovolemic Shock, Volume Resuscitation, and Vasoconstriction. Mil Med. 2023 Nov 8;188(Suppl 6):369-376.
17. Al Tayar, A.; Abouelela, A.; Mohiuddeen, K. Can the cerebral regional oxygen saturation be a perfusion parameter in shock? J Crit Care. 2017 Apr: 38:164-167.
18. Balakrishnan, B., Dasgupta, M., Gajewski, K., Hoffmann, R. G., Simpson, P. M., Havens, P. L. et. al. Low near-infrared spectroscopic somatic oxygen saturation at admission is associated with need for lifesaving interventions among unplanned admissions to the pediatric intensive care unit. J Clin Monit Comput. 2018 Feb;32(1):89-96.
19. Lima, A., van Bommel, J., Jansen, T. C., Ince C, Bakker J. Low tissue oxygen saturation at the end of early goal-directed therapy is associated with worse outcome in critically ill patients. Crit Care.2009;13 Suppl 5(Suppl 5): S13.
20. Vorwerk C, Coats TJ. The prognostic value of tissue oxygen saturation in emergency department patients with severe sepsis or septic shock. Emerg Med J. 2012 Sep;29(9):699-703.
21. Austin EH 3rd, Edmonds HL Jr, Auden SM, Seremet V, Niznik G, Sehic A et. al. Benefit of neurophysiologic monitoring for pediatric cardiac surgery. J Thorac Cardiovasc Surg. 1997 Nov;114(5):707-15, 717; discussion 715-6.
22. Kamba, M., Sung YW, Ogawa S. Alteration of blood oxygenation level-dependent signaling by local circulatory condition. J Magn Reson Imaging. 2007 Dec;26(6):1506-13.
23. Bartocci, M., Winberg, J., Papendieck, G., Mustica, T., Serra G, Lagercrantz H. Cerebral hemodynamic response to unpleasant odors in the preterm newborn measured by near-infrared spectroscopy. Pediatr Res. 2001 Sep;50(3):324-30.
24. Lemmers P, Van Bel F. Left-to-right differences of regional cerebral oxygen saturation and oxygen extraction in preterm infants during the first days of life. Pediatr Res. 2009 Feb;65(2):226-30.
25. Kussman, B. D., Wypij, D., DiNardo, J. A., Newburger, J., Jonas, R. A., Bartlett, J. et. al. An evaluation of bilateral monitoring of cerebral oxygen saturation during pediatric cardiac surg Anesth Analg. 2005 Nov;101(5): 1294-1300.ery.
26. Öztürk, N. Y., Aygün, B., Uyar, E., & Girgin, F. İ. Comparison of Bilateral Cerebro-Renal Tissue Oxygenations in Healthy Children. Indian J Pediatr. 2020 Feb;87(2):99-10

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RESEARCH ARTICLE

Evaluation of Complete Blood Count Parameters in Patients with Methylmalonic Acidemia

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ABSTRACT

Objective: We aimed to evaluate the frequency of pathological changes in blood parameters and their relationship with serum creatinine and glomerular filtration rate (GFR) in patients with methylmalonic acidemia.
Methods: Demographic and laboratory data of 46 patients diagnosed by acylcarnitine, urine organic acid, and/or molecular analyses for methylmalonic acidemia were evaluated. In all patients, complete blood counts, serum iron concentrations, serum iron-binding capacity, vitamin B12 and folate concentrations, and serum creatinine tests were performed during the period when the patients were metabolically stable.
Results: Among the 46 patients with anaemia, 54.3% had anaemia of chronic disease, 19.6% had iron deficiency anaemia. Bicytopenia was detected in 17.4%. There was a negative correlation between serum creatinine levels and leucocyte, lymphocyte, erythrocyte, and platelet counts. GFR values were positively correlated with haemoglobin value, leukocyte, lymphocyte, erythrocyte, and platelet counts.
Conclusions: The presence of anaemia, neutropenia, thrombocytopenia, and erythrocyte volume changes in patients with methylmalonic acidemia apart from the metabolic attack period is a situation that reveals the necessity of a detailed nutritional evaluation of patients. Evaluation of renal function in the presence of haematological complications and taking precautions if signs of renal failure are noted may prevent worsening of complications.

Keywords: Methylmalonic acidemia, anemia, thrombocytopenia, renal failure, bone marrow

INTRODUCTION

Methylmalonic aciduria is a disorder of methylmalonic acid (MMA) and cobalamin (cbl) metabolism that can be caused by different genetic problems. Isolated methylmalonic aciduria is usually a result of partial [mut (-)] or complete [mut (0)] deficiency of methylmalonyl-CoA mutase, a mitochondrial enzyme caused by mutations in the MUT gene (1). However, cblA, cblB, and cblD deficiencies leading to metabolic problems in the synthesis or transport of adenosyl-cobalamin, the cofactor of methylmalonyl-CoA mutase, can cause isolated methylmalonic acidemia. In cblC, cblD, and cblF deficiencies, which are among the disorders of cobalamin metabolism, methylmalonic aciduria and homocystinuria are observed together.

Patients usually develop lethargy, tachypnoea, vomiting, dehydration, acute metabolic acidosis, ketosis, and hyperammonemia shortly after birth. In the absence of appropriate treatment, coma and death due to hyperammonemic encephalopathy may occur. If patients survive the first metabolic attack, recurrent episodes of metabolic decompensation triggered by catabolic processes, including infection, vaccination, and teething, are observed during follow-up (2). Haematological abnormalities including anaemia, leukopoenia, neutropenia, thrombocytopenia, and pancytopenia, are detected especially during metabolic attacks caused by bone marrow suppression. In most patients, multisystem complications secondary to methylmalonic aciduria, including developmental delay, optic atrophy, and renal impairment, develop (2). It has been suggested that secondary metabolic changes triggered by the accumulation of toxic metabolites, including propionyl-CoA, 2-methylcitric acid, and MMA, are among the causes of these long-term abnormalities (2).

Individuals with isolated methylmalonic aciduria are at risk of renal failure (3). The course of chronic renal failure is worsened by secondary complications of renal failure such as anaemia, arterial hypertension, renal osteodystrophy, and hyperparathyroidism (4). Patients with chronic kidney disease may not be able to use the iron stores in their body effectively and therefore may require additional iron therapy. With further deterioration of renal function, erythropoietin

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production in the kidneys may decrease, and patients may require erythropoietin treatment (5).

Anaemia, leucopoenia and thrombocytopenia have been reported during acute metabolic decompensation in patients with methylmalonic acidemia, propionic acidemia, or isovaleric acidemia (6). In this study, we aimed to evaluate the variety and frequency of pathological changes in blood parameters and the relationship between these changes and serum creatinine and glomerular filtration rate (GFR) in patients with methylmalonic acidemia during periods when they did not experience metabolic attacks.

MATERIALS AND METHODS

The demographic and laboratory characteristics of 46 patients who were diagnosed as having an acylcarnitine profile by tandem mass spectrometry (MSMS), organic acid profile by gas chromatography-mass spectrometry (GC-MS), and/or methylmalonic acidemia by molecular analysis between 1995 and 2022 in the Department of Paediatric Nutrition and Metabolism, Istanbul Faculty of Medicine were evaluated. The Ethics Committee of Istanbul Faculty of Medicine approved the study (file number 2023/1500, date: 25/08/23). Written informed consent was obtained from all participants or their legal guardians after the study procedure was explained.

In all patients, complete blood count, serum iron concentration, serum iron binding capacity, vitamin B12 and folate concentrations, and serum creatinine tests performed using conventional methods during the period when the patients were metabolically stable were evaluated from the file notes. A haemoglobin value below the 5th percentile of the normal value determined for that age (7), a serum ferritin value < 12 mcg/L below the age of 5 years and < 15 mcg/L above the age of 5 years (8), and a transferrin saturation below 15% have been accepted as iron deficiency anaemia (9). Chronic disease anaemia has been defined with decreased plasma iron concentration, decreased total iron binding capacity, decreased transferrin saturation, and normal or increased ferritin concentration (10). While cytopenia in two blood cell populations is defined as bicytopenia, the combination of anaemia, neutropenia, and thrombocytopenia is defined as pancytopenia. The glomerular filtration rate (GFR) was calculated using the Schwartz formula. The stages of renal failure were determined according to the glomerular filtration rates of the patients (11).

Mean, standard deviation, median, minimum, maximum, and ratio values were used in the descriptive statistics of the data. The distribution of variables was measured using the Kolmogorov–Smirnov test. The Spearman correlation analysis test was used to analyse quantitative independent data. SPSS 28.0 software was used in the analyses.

RESULTS

The mean age was 14.7±8.7 (median: 13.1, range: 1-41.1) years in 46 patients, including 31 males and 15 females from 37 families. The mean follow-up period was 14.5±7.5 (range: 11 months-28.7 years; median: 13.1 years). Extended newborn screening was the diagnostic method for three patients within the first month of life. Due to sibling history, 3 patients were diagnosed in the first week of life, 1 patient in the prenatal period, and one at 13 years of age. Thirty-eight patients were diagnosed due to symptomatic presentation. Fifteen symptomatic patients were diagnosed within the first month of life. The age at symptomatic presentation ranged from 1 month to 6 years (median 2 years) (Table 1).

Of the 46 patients with anaemia, 25 (54.3%) had anaemia of chronic disease and 9 (19.6%) had iron deficiency anaemia. Bicytopenia was found in 8 (17.4%) of 46 children. Among these, anaemia and thrombocytopenia were found in 2 children, anaemia and neutropenia in 4 children, anaemia and lymphopenia in 1 child, and thrombocytopenia and lymphopenia in 1 child. No patient had pancytopenia.

When renal failure was evaluated according to glomerular filtration rate, stage 1 renal failure was found in 27 patients, stage 2 renal failure in 8 patients, stage 3 renal failure in 7 patients, and stage 4 renal failure in 4 patients. Age was positively correlated with serum creatinine levels and negatively correlated with GFR, leucocyte, lymphocyte, and platelet counts. There was a negative correlation between serum creatinine levels and leucocyte, lymphocyte, erythrocyte, and platelet counts. GFR values were positively correlated with haemoglobin value, leukocyte, lymphocyte, erythrocyte, and platelet counts (Table 2).

DISCUSSION

In patients with methylmalonic acidemia and other organic acidemias, cytopenia is a condition that usually occurs during periods of acute decompensation. However, patients may also experience anaemia, neutropenia, or thrombocytopenia outside these periods. The pathophysiology underlying bone marrow involvement in methylmalonic acidemia is thought to involve multiple factors, such as the direct toxic effect of accumulated organic acids and other metabolites, micronutrient deficiencies, and complex mitochondrial dysfunction, which are related to impaired energy production and oxidative stress (6, 12, 13).

Although anaemia, neutropenia, thrombocytopenia, and pancytopenia have been frequently evaluated in propionic acidemia, few studies have evaluated the prevalence of these complications in patients with MMA. Kölker et al. reported that the mean haemoglobin level in patients with MMA was 40% below the reference range. On average, the leukocyte count of patients was 7% below the reference range. The platelet count was 6% below the reference range in patients with MMA (14). Another study reported that 37 (28.0%) of 132 patients diagnosed with cobalamin C deficiency had anaemia (15). Leukopoenia was found in 21/35, anaemia in 11/33, and thrombocytopenia in 15/30 of 45 patients with isolated methylmalonic acidemia (16). In Tavil et al. an anaemia was found in all 11 patients with a diagnosis of MMA, and one of them was reported to have pancytopenia. Anaemia

Table 1: Demographic data and complete blood count parameters of patients with methylmalonic acidemia.

Patient	Gender	Diagnosis method	Age at diagnosis	Follow-up (years)	Renal Insufficiency stage	Hb (g/dl)	PLT (10^3/µl)	PNL (10^3/µl)
1	M	Symptomatic	1 m	7.1	1	13.6	351	3.5
2	M	Symptomatic	1 m	6.2	1	13.2	469	3.2
3	M	Symptomatic	1 m	13.1	1	10.4	142	3.6
4	F	Sibling history	1 m	26.5	1	10.2	205	4.7
5	M	Symptomatic	1 m	9.2	1	12.8	337	3.9
6	F	Symptomatic	1 m	3.4	1	12.3	431	2.7
7	M	Symptomatic	1 m	10.1	1	12.6	379	4.2
8	M	Symptomatic	1 m	11.7	1	10.9	330	4
9	M	Symptomatic	3 m	8.2	1	14	296	4.7
10	M	NBS	1 m	9.6	1	14.2	381	3.7
11	F	Symptomatic	10 m	16.7	1	14.6	186	3.1
12	F	Symptomatic	1 m	7.8	1	14.1	325	6.1
13	F	NBS	1 m	13.5	1	11.6	259	4.6
14	M	Symptomatic	6 y	26	1	16.4	255	5.2
15	M	Symptomatic	1 m	0.8	1	11.5	284	3.5
16	M	Symptomatic	1 m	1.5	1	8.9	494	1.9
17	F	Symptomatic	2 m	9.6	1	10.1	355	7.8
18	M	Symptomatic	7 m	7.8	1	12	284	10.4
19	F	Symptomatic	2 m	7.2	1	9.9	389	5.1
20	M	Symptomatic		6.5	1	13.9	241	3.1
21	M	Symptomatic	8 m	12.7	1	11.4	280	3.4
22	M	Symptomatic	8 m	15	1	14.6	293	4.1
23	F	Symptomatic	1 m	13.1	1	13.8	317	5.8
24	M	Sibling history	1 m	11.7	1	37	207	5.3
25	M	NBS	1 m	10.3	1	12.3	331	5.1
26	F	Symptomatic	1 m	0.9	1	9.25	179	1.64
27	F	Symptomatic	15 m	16.3	1	12	216	3.1
28	M	Sibling history	1 m	4.9	2	8.6	275	5
29	M	Symptomatic	4 m	23.3	2	11.1	159	2
30	M	Symptomatic	1 m	22.5	2	12.2	162	2.5
31	M	Symptomatic	8 m	5.6	2	9.3	268	2
32	M	Symptomatic	1.5 y	11	2	8.2	225	6
33	M	Symptomatic	22 m	17.1	2	17.5	250	5.9
34	F	Symptomatic	1 m	28.7	2	10	262	4.5
35	F	Symptomatic	6 m	19.3	2	11	141	2.8
36	F	Symptomatic	1 m	14.6	3	11.7	190	1.3
37	M	Symptomatic	1 m	17.0	3	10.5	167	2
38	M	Symptomatic	2 m	23	3	13	332	3.1
39	M	Sibling history	13 y	28.1	3	15.3	245	5.6
40	M	Symptomatic	5 m	22.1	3	10	197	2.6

Table 1: Continued.

Patient	Gender	Diagnosis method	Age at diagnosis	Follow-up (years)	Renal Insufficiency stage	Hb (g/dl)	PLT (10^3/µl)	PNL (10^3/µl)
41	M	Sibling history	1 m	10.7	3	11.9	204	3.8
42	M	Symptomatic	2 m	23	3	11	337	2.6
43	M	Symptomatic	4 m	23.4	4	9.9	199	1.8
44	F	Symptomatic	5 m	19.9	4	6.5	125	1.7
45	M	Symptomatic	15 m	22	4	11	202	4.2
46	F	Symptomatic	3 m	26	4	10.2	362	5

F: Female, M: Male, NBS: Newborn screening, Hb: Haemoglobin, PLT: Platelet, PNL: Polymorph nuclear leucocytes; m: months, y: years; *prenatal diagnosis

Table 2: Correlations of age, serum creatinine level, glomerular filtration rate, and complete blood count parameters in patients with methylmalonic acidemia

		Age	Cr	GFR	Hb	PLT	PNL	LYM	Leu	RBC
Age	**CC**	1,000	,737**	-,555**	0,025	-,449**	-0,007	-,705**	-,455**	-0,036
	p		0,000	0,000	0,869	0,002	0,961	0,000	0,001	0,815
Cr	**CC**	,737**	1,000	-,917**	-0,171	-,488**	-0,135	-,553**	-,479**	-,302*
	p	0,000		0,000	0,256	0,001	0,370	0,000	0,001	0,044
GFR	**CC**	-,555**	-,917**	1,000	,301*	,431**	0,213	,355*	,361*	,403**
	p	0,000	0,000		0,047	0,004	0,165	0,020	0,016	0,007
Hb	**CC**	0,025	-0,171	,301*	1,000	0,185	,317*	0,026	0,165	,820**
	p	0,869	0,256	0,047		0,217	0,032	0,867	0,272	0,000
PLT	**CC**	-,449**	-,488**	,431**	0,185	1,000	,338*	,381**	,463**	,316*
	p	0,002	0,001	0,004	0,217		0,022	0,010	0,001	0,035
PNL	**CC**	-0,007	-0,135	0,213	,317*	,338*	1,000	0,005	,596**	,306*
	p	0,961	0,370	0,165	0,032	0,022		0,976	0,000	0,041
LYM	**CC**	-,705**	-,553**	,355*	0,026	,381**	0,005	1,000	,560**	-0,022
	p	0,000	0,000	0,020	0,867	0,010	0,976		0,000	0,886
Leu	**CC**	-,455**	-,479**	,361*	0,165	,463**	,596**	,560**	1,000	0,176
	p	0,001	0,001	0,016	0,272	0,001	0,000	0,000		0,248
RBC	**CC**	-0,036	-,302*	,403**	,820**	,316*	,306*	-0,022	0,176	1,000
	p	0,815	0,044	0,007	0,000	0,035	0,041	0,886	0,248	

Cr: Serum creatinin, GFR: Glomerular filtration rate, Hb: Haemoglobin, PLT: Platelet, PNL: Polymorph nuclear leucocytes, LYM: Lymphocyte, Leu: Leucocyte, RBC: Erythrocyte, CC: Correlation coefficient, p: 2-tailed significance; *Correlation is significant at 0.05, **Correlation is significant at 0.01

was evaluated as chronic disease in eight patients and iron deficiency in two (17). As observed in other case series of patients with methylmalonic acidemia, anaemia was found at a high rate in our patient group. Anaemia was found in 34 (73.9%) patients, 25 of whom were evaluated as anaemia of chronic disease and 9 were evaluated as iron deficiency anaemia. This situation reveals that anaemia is a frequent morbidity and should be emphasised sensitively during follow-up of patients. Two patients whose blood samples were evaluated outside the acute metabolic attack period had anaemia and thrombocytopenia, four had anaemia and neutropenia, one had anaemia and lymphopenia, and one had lymphopenia and thrombocytopenia. Low blood cell counts in patients outside the metabolic attack period are associated with metabolite accumulation, nutrient deficiencies, and mitochondrial dysfunction (6, 12, 13). Therefore, blood count parameters should be considered as an important factor in patient follow-up and treatment organisation.

It is known that bone marrow function in patients with renal failure is suppressed, iron stores cannot be effectively used, and haematological complications occur with decreased erythropoietin production as renal failure progresses (5). When renal failure and blood parameters of patients followed up with a diagnosis of methylmalonic acidemia were examined, GFR was positively correlated with haemoglobin concentration, erythrocyte count, platelet count, leukocyte count, and lymphocyte count. Serum creatinine levels were negatively

correlated with erythrocyte, leukocyte, lymphocyte, and platelet counts. Anaemia was detected in eight of the 11 patients with stage 3 and 4 renal failure. Patients with methylmalonic acidemia should be carefully monitored for the development of anaemia, especially after renal function begins to be affected. Renal failure should be taken into consideration when designing treatment for anaemia, and different treatment options should be evaluated.

The fact that the study was conducted in a single centre is a limitation factor in terms of reflecting the practises of only one centre. The small number of patients is another limitation.

CONCLUSION

Patients diagnosed with organic acidemia frequently present with pancytopenia requiring blood transfusion during metabolic decompensation, which resolve spontaneously within a few weeks (18). In cases of resistant pancytopenia, it is important to exclude other bone marrow pathologies, such as hypoplasia, aplasia, hemophagocytic lymphohistiocytosis, and myelodysplastic syndrome. In addition, because blood tissue has a high regeneration rate, its nutrient requirements are higher than those of other tissues. This situation causes haematopoietic tissue to be easily affected by nutritional deficiencies (19). In patients, nutrient deficiencies may develop because special nutritional therapies are applied in which natural protein intake is restricted and protein intake is interrupted during metabolic attack periods to prevent the accumulation of toxic substances (20). We believe that the presence of anaemia, neutropenia, thrombocytopenia, and erythrocyte volume changes in patients with methylmalonic acidemia outside the metabolic attack period is a condition that highlights the necessity of detailed nutritional evaluation of patients. Evaluation of renal function in the presence of haematological complications in patients with methylmalonic acidemia and taking precautions when signs of renal failure are present may be a step to prevent worsening of complications. Further research is needed to better understand the mechanisms underlying haematological complications in this patient group and to develop effective treatments for these patients.

Ethics Committee Approval: This study was approved by the ethics committee of Istanbul Faculty of Medicine approved the study (file number 2023/1500, date: 25/08/23).

Informed Consent: Written consent was obtained from all participants or their legal guardians.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- M.C.B., M.K., G.F.G.; Data Acquisition- - M.C.B., M.K., G.F.G.; Data Analysis/ Interpretation- - M.C.B., M.K., G.F.G.; Drafting Manuscript-- M.C.B., M.K., G.F.G. ; Critical Revision of Manuscript- - M.C.B., M.K., G.F.G.; Final Approval and Accountability- - M.C.B., M.K., G.F.G.

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REFERENCES

1. Dionisi-Vici C, Deodato F, Röschinger W, Rhead W, Wilcken B. Classical organic acidurias, propionic aciduria, methylmalonic aciduria, and isovaleric aciduria: long-term outcome and effects of expanded newborn screening using tandem mass spectrometry. J Inherit Metab Dis. 2006;29(2-3):383-9.
2. Zwickler T, Haege G, Riderer A, Hörster F, Hoffmann GF, Burgard P et al. Metabolic decompensation in methylmalonic aciduria: which biochemical parameters are discriminative? J Inherit Metab Dis. 2012;35(5):797-806.
3. Morath MA, Hörster F, Sauer SW. Renal dysfunction in methylmalonic acidurias: review for the paediatric nephrologist. Pediatr Nephrol. 2013;28(2):227-35.
4. Hörster F, Baumgartner MR, Viardot C, Suormala T, Burgard P, Fowler B, et al. Long-term outcome in methylmalonic acidurias is influenced by the underlying defect (mut0, mut-, cblA, cblB). Pediatr Res. 2007;62(2):225-30.
5. Mikhail A, Brown C, Williams JA, Mathrani V, Shrivastava R, Evans J et al. Renal association clinical practise guideline on Anaemia of Chronic Kidney Disease. BMC Nephron. 2017;18(1):345.
6. Inoue S, Krieger I, Sarnaik A, Ravindranath Y, Fracassa M, Ottenbreit MJ. Inhibition of bone marrow stem cell growth in vitro by methylmalonic acid: a mechanism of pancytopenia in patients with methylmalonic acidemia. Pediatr Res. 1981;15(2):95-8.
7. Orkin SH ND, Ginsburg D, Look AT, Fisher DE, Lux S. Nathan and Oski's haematology of infancy and childhood. 8th ed. Philadelphia: Saunders; 2015.
8. WHO, UNICEF, UNU. Guideline: daily iron supplementation in infants and children. 2016
9. Auerbach M, Adamson JW. How to diagnose and treat iron deficiency anaemia. Am J Hematol. 2016;91(1):31-8.
10. Ezekowitz, R.A.S.J. Haematologic manifestations of systemic diseases. In: Nathan DG OS, Ginsburg D, Look AT. Haematology of Infancy and Childhood. Philadelphia: W. B. Saunders; 2003. p. 1771–2.
11. Webster AC, Nagler EV, Morton RL, Masson P. Chronic Kidney Disease. Lancet. 2017;389(10075):1238-52.
12. Chandler RJ, Zerfas PM, Shanske S, Sloan J, Hoffmann V, DiMauro S et al. Mitochondrial dysfunction in mut methylmalonic acidemia. Faseb j. 2009;23(4):1252-61.
13. Kölker S, Burgard P, Sauer SW, Okun JG. Current concepts in organic aciduria: understanding intra- and extracerebral disease manifestation. J Inherit Metab Dis. 2013;36(4):635-44.
14. Kölker S, Valayannopoulos V, Burlina AB, Sykut-Cegielska J, Wijburg FA, Teles EL, et al. Phenotypic spectrum of organic aciduria and urea cycle disorders. Part 2: the evolving clinical phenotype. J Inherit Metab Dis. 2015;38(6):1059-74.
15. He R, Mo R, Shen M, Kang L, Song J, Liu Y et al. Variable phenotypes and outcomes associated with the MMACHC c.609G>A homologous mutation: long-term follow-up in a large cohort of cases. Orphanet J Rare Dis. 2020;15(1):200.
16. Matsui SM, Mahoney MJ, Rosenberg LE. Natural history of the inherited methylmalonic acidemias. N Engl J Med. 1983;308(15):857-61.
17. Tavil B, Sivri HS, Coskun T, Gurgey A, Ozyurek E, Dursun A et al. Haematological findings in children with inborn errors of metabolism. J Inherit Metab Dis. 2006;29(5):607-11.

18. Bakshi NA, Al-Anzi T, Mohamed SY, Rahbeeni Z, AlSayed M, Al-Owain M et al. Spectrum of bone marrow pathology and haematological abnormalities in methylmalonic acidemia. Am J Med Genet A. 2018;176(3):687-91.
19. Santos EW, Oliveira DC, Silva GB, Tsujita M, Beltran JO, Hastreiter A et al. Haematological alterations in protein malnutrition. Nutr Rev. 2017;75(11):909-19.
20. Daly A, Evans S, Gerrard A, Santra S, Vijay S, MacDonald A. Nutritional Intake of Patients with Organic Acidemia on Enteral Tube Feeding: Can We Do Better? JIMD Rep. 2016;28:29-39.

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RESEARCH ARTICLE

Factors Affecting Thyroid Volume and the Incidence of Nodules With Goiter School-Aged Children

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ABSTRACT

Objective: This study aimed to analyze the associations between age, sex, anthropometric factors, and thyroid volume as well as to determine the prevalence of goiter and thyroid nodules in school children.
Methods: This study included schools governed by the Ministry of Education in Van province. Sonographic evaluations of thyroid glands were conducted in children aged 6–17 years, and measurements of weight, height, waist circumference, hip circumference, and skinfold thickness were obtained from the participants.
Results: A total of 2284 school children were included in the study. The median age of the participants was 11.08 years. It was observed that thyroid volume exhibited a positive correlation with age, body surface area, body mass index, height, weight, waist circumference, hip circumference, triceps skinfold thickness, and subscapular skinfold thickness ($p < 0.008$). When assessing the association between age and goiter prevalence based on World Health Organization parameters, 10.2% of children and adolescents developed goiter, and 0.8% of these cases also had a nodule. Among girls, the rates were 9.4% and 1% for goiter and nodules, respectively, whereas among boys, the rates were 11.3% and 0.7%, respectively.
Conclusions: Thyroid volume was affected by age, weight, subcutaneous tissue thickness, waist circumference, and BSA. Goiter remains a serious public health problem among school-age children in Van province.

Keywords: Anthropometry, Child; Goiter, Nodule, Thyroid

INTRODUCTION

Thyroid diseases are common endocrine disorders in children and adolescents. Iodine deficiency disorder (IDD) is a common public health issue, as it is the primary cause of preventable mental retardation and permanent brain damage in fetuses, infants, and children (1,2). However, iron, selenium, vitamin A, and zinc may interact with iodine and thyroid function (3). It has been demonstrated that protein-energy malnutrition (PEM) is a contributing factor to endemic goiter in children (4,5). Although international public health efforts have proven highly effective over the past several decades, nearly one-third of children worldwide remain at risk of iodine deficiency (6). Despite the Health Ministry's initiation of a national program that includes iodized salt standardization and its widespread use and the implementation of legislation mandating the iodization of household salt in 1998 in Turkey, endemic goiter and iodine deficiency continue to pose significant public health concerns (7,8). The prevention and control of iodine deficiency are ongoing; however, no new iodination studies have been conducted in our region since then. Therefore, a comprehensive iodination program is planned to be implemented by reviewing existing programs in Van province. Although urinary iodine concentration (UIC) can adequately assess a population's iodine nutrition, it does not provide conclusive information about an individual's iodine levels. Conversely, thyroid volume (Tvol) is an indicator of individual iodine status.

Ultrasonographic examination of the thyroid gland provides precise information on thyroid volume (Tvol), making it the most reliable method for thyroid volume assessment. Tvol is correlated with age, sex, and body surface area (BSA) (9).

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However, different studies have highlighted various influencing factors, leading to ongoing debate. Although urinary iodine concentration (UIC) effectively assesses the iodine nutritional status of a population, it does not reflect individual iodine levels. Conversely, Tvol indicates an individual's iodine status but is also subject to confounding factors. Childhood thyroid nodules though rare, have a significant malignancy rate of up to 25%.

There is a scarcity of epidemiological studies on thyroid nodules among pediatric patients. No study has been conducted on factors influencing thyroid volume, goiter, and nodule prevalence in school-age children using ultrasound in this region of Turkey. For the aforementioned reasons, we aimed to investigate the associations among age, gender, anthropometric measurements (weight, height, waist circumference, hip circumference, and skinfold thickness), thyroid volume, and the prevalence of goiter and thyroid nodules among school-age children.

MATERIALS AND METHODS

The study was approved by the Ethical Committee of Van Yüzüncü Yıl University **(Decision No: 25, Date: 05.09.2013)**. Only participants who provided a written informed consent document, which was approved by their parents and school guardian, were included in the study.

The study included state schools in both rural and urban areas. Written and verbal information was provided to 5000 students, and consent forms were sent to their home addresses to obtain parental consent.

The exclusion criteria were as follows:

1. Children taking glucocorticoids, dopamine, dobutamine, or antiepileptic drugs (such as phenytoin, carbamazepine, or others).
2. Those who had received amiodarone or an iodine-containing contrast agent within the prior 6 months.
3. Children with adrenocortical, renal, or other serious systemic or chronic wasting diseases.
4. Patients with a known thyroid disease or a history of thyroid disease.

Overall, 2284 students from 9 separate schools governed by the Ministry of Education in Van province were included in this study. The study team consisted of 6 persons including a radiologist, a pediatry residence and 4 healthcare professionals. They were trained in the techniques and standardization of the methods used. The team and equipment attended the school at 07:30 AM. Measurements were performed between 08:00 and 12: AM. In all participants, anthropometric measurements (weight, height, waist and hip circumference, subscapular skinfold thickness [SST], triceps skinfold thickness [TST]) and thyroid ultrasonography were performed. Individual procedures were performed by the same person throughout the study.

The date of birth, gender, and age were recorded for all students. Anthropometrics was performed before ultrasonography. Weight was measured using a NAN device (İstanbul) sensitive to 50 g. Body weight was measured without shoes, with only thin clothes on the arms parallel to the body and in the neutral position. The result seen as "kg" was taken as the result. Height was measured using a Seca stadiometer at a 90° angle to the floor according to the parameters established by Jelliffe and the World Health Organization (WHO) (10). Body mass index (BMI) was measured using the formula: weight (kg)/ Height^2 (m^2). BSA was calculated using the Du Bois formula: BSA = Weight (kg)$^{0.425}$x Height (cm)$^{0.725}$x71.84x10^{-4} (11). Waist circumference (WC) was measured using an inelastic tape measure at the level in the middle of distance between the last rib and the iliac crest (12) Hip circumference (HC) was measured at the level of highest protuberance in the gluteal region using an inelastic tape measure. The WC and HC were recorded in centimeters. Skinfold thickness was measured at the left subscapular region and left arm using a device and expressed as "mm". The clothes of the patients were removed during the measurements. Triceps and subscapular skinfold thicknesses were measured in triplicate on the left side of the body to the nearest 0.1 mm using a Harpenden caliper in accordance with the standardized techniques recommended by Lohman et al. (13). The mean of triplicate values was used in the analysis.

Thyroid volume and the presence of nodules were examined using Philips HD-11 ™ US unit with a 7.5-MHz transducer/ probe (Bothell, Washigton, USA). All measurements were performed by a single radiologist. On-screen measurements were verified by printing copies of the images, which were later measured by a second technician using handheld calipers. The nodule diameter of >5 mm was considered to indicate a true nodular appearance. In clinical practice, fine needle biopsy is not recommended for nodules smaller than 5 mm. Thus, nodules smaller than 5 mm were not evaluated by US. The volume of each lobe was calculated using the equation described by Brunn et al.: Volume of lobe = depth ×width length (cm) × 0.479. The thyroid gland volume (TTV) is the sum of the volume of each lobe. The isthmus volume was excluded. Thyroid volumes greater than the 97th percentile (WHO/ICCIDD) were considered abnormally enlarged (14,15). Thyroid size was assessed according to the WHO staging (16).

Statistical Analysis

Data were analyzed using SPSS for Windows version 13 (Statistical Package for Social Sciences). Frequency, mean, median, SD, 97th percent values with 95% confidence intervals (CIs) were measured in the entire population, in individual pediatric subgroups, and in subgroups stratified by other parameters, such as anthropometrics, thyroid volume, nodule presence rate, goiter presence frequency, and BMI. The independent sample t-test was used to compare independent groups. The correlation between thyroid volume and anthropometric measurements was determined using multiple linear regression analysis. Comparisons between subgroups were performed using the chi-square test and

Kruskal–Wallis test, and correlation analysis was performed using Spearman correlation analysis, and the threshold for statistical significance was α = 0.05. Pearson's correlation analysis was performed to examine the relationship between the independent variables.

RESULT

The final study cohort consisted of 2284 school children. The mean age of the subjects was 11.4±3,13 (6-17 years), and the median age was 11.08. There were 1006 (44%) boys and 1278 (56%) girls in the cohort. Table 1 presents the anthropometric and thyroid volume data of the study cohort. Thyroid volume increased with advancing age (r=0,986, p=0,000 pearson correlation), with higher volumes observed in girls than boys (p=0,700, independent t test). Thyroid volume was significantly greater in girls in age group of 12-13 years (p<0.05, p<0.01) (Table 1). Table 2 presents the median, mean, standard deviation, and 97th percentile (p) values of thyroid volume according to age and gender.

When the multiple linear regression analysis was performed between thyroid volume and anthropometrics, thyroid volume showed a positive correlation with age, BSA, BMI, height, weight, waist circumference, hip circumference, TST, and SST (Sig. (2-tailed) < 0,008) (Table 4). Table 4 presents the distribution of thyroid volumes according to BSA and sex. When thyroid volumes according to BSA were compared with regard to sex, it was seen that thyroid volume was greater in girls with BSA levels between 1.3 and 1.5 m^2 (p> 0,005, p<0.001 and p<0.010, respectively).

This ratio was 9.4% and 1% for girls and 11.3% and 0.7% for boys, respectively. There was no significant difference according to sex when all age groups were evaluated for the prevalence of goiter and nodules. However, goiter was more prevalent in girls in age group of 6-9 years age when age groups were evaluated individually (p<0.05) (Table 5).

Goiter was detected in 19.1% of boys and 11.5% of girls when the goiter prevalence according to BSA was analyzed based on the goiter limits proposed by WHO. Goiter prevalence was significantly higher in boys with BSA of 0.9-1.2 m^2 and was statistically significantly more prevalent in boys than girls (p<0.010, p<0.001, p<0.010 and p<0.010, respectively (Table 6).

DISCUSSION

Population iodine status is most commonly assessed using median urinary iodine concentrations, but goiter prevalence (determined by palpation or by ultrasound), serum thyroglobulin levels, and neonatal thyroid-stimulating hormone levels can also be used. In areas of mild-to-moderate IDDs, the sensitivity and specificity of palpation are poor (17), and measurement of thyroid volume (Tvol) by ultrasound is preferable, non-invasive, rapid (2–3 min per subject), and feasible even in remote areas by using portable equipment, and it is accepted as a standard method for measuring thyroid volume (18). In the present study, we also investigated some factors that affect thyroid volume. It was found that thyroid volume was higher in girls, although it has been reported that thyroid volume does not differ according to sex (19). There are also studies reporting higher thyroid volumes in females (20). It is obvious that the relationship between thyroid volume and gender are controversial. We think that higher thyroid volumes in age group of 12-13 years and BSA of 1.3-1.5 m^2 can be attributed to accelerated somatic growth during puberty (21).

Table 1. Shows the distribution median values of anthropometrics and thyroid volume according to sex

	n		Height (cm)		Weight (kg)		Waist C. (cm)		Hip C. (cm)		TST (cm)		SST (cm)		BMI (kg/m^2)		BSA		Right TLV (cm^3)		Left TLV (cm^3)		Total TV (cm^3)	
Age (yr)	B	G	B	G	B	G	B	G	B	G	B	G	B	G	B	G	B	G	B	G	B	G	B	G
6	70	86	118	119	22	21	54	53,5	61	62	10¥	10	6*	6	22	21	0,83	0,84	2,09	2,13	2,21	2,21	4,40	4,37
7	83	103	121	122	23	23	54	55	63	63	9¥	11	5*	7	23	23	0,89	0,88	2,08	2,33	2,25	2,34	4,36	4,59
8	113	113	130	128	27	26	57	56	66	67	9¥	11	6¥	7	27	26	0,97	0,96	2,4	2,54	2,54	2,80	4,97	5,29
9	113	167	130	130	28	27	56	57	68	67	9¥	10,5	6*	8	28	27	1,02	1	2,60	2,55	2,61	2,60	5,26	5,27
10	118	138	136	139	30	30	57,5	58	70	70	9¥	10	6*	7	30	30	1,09	1,1	2,85	2,88	2,73	2,76	5,61	5,71
11	110	130	140	144	33	34,5	60	60	73	72	9¥	10	6¥	8	33	34,5	1,14	1,19	3,13	3,14	3,07	3,19	6,31	6,55
12	74	108	148	150	38	39,5	63	62	75*	78	9,5¥	10	6,5¥	8	38	39,5	1,28	1,31	3,25*	3,64	3,18	3,39	6,35*	7,01
13	81	93	152	155	40¥	46,5	60*	65	76£	83	9£	11	6£	9	40¥	46,5	1,3£	1,42	3,62¥	3,86	3,47*	3,75	7,04¥	7,92
14	81	105	158	157	46,5	49	65,5	65	81¥	85	9,5£	14	7£	10,5	46,5	49	1,44	1,46	3,95	4,10	3,82	3,92	7,77	8,22
15	51	105	162£	157	53	50	68	67	87	87	10£	14	7£	11	53	50	1,58¥	1,49	4,49	4,52	4,35	4,20	8,79	8,79
16	60	74	166£	157	55£	49	69	67	87	86	9£	12	6£	10	55¥	49	1,63£	1,47	4,73	4,88	4,56	4,37	8,98	9,33
17	51	55	164¥	157	53	53	69,5	71,5	86	89,5	9£	15	7£	12	53	53	1,57	1,51	4,65	4,72	4,61	4,64	9,65	9,76

SST: Subscapular skin thickness; TST: Triceps skin thickness; C: Circumference; BMI: Body mass index; BSA: Body surface area; TLV: trois lobe volüme; B. boys, G: Girls, *:p<0,05; ¥:<0,01; £: p<0,001, superscript letters show comparison of each parameter in each age group with regard to gene.

Table 2. Range, mean, median, and standard deviation of thyroid gland volume according to age and gender

			Right thyroid lobe (cm_3)				Left thyroid lobe (cm_3)				Total thyroid volume (cm_3)			
Age (yr)		**N**	**mean**	**SD**	**median**	**97p**	**mean**	**SD**	**median**	**97p**	**mean**	**SD**	**median**	**97p**
6	**Boys**	70	2,23	0,68	2,09	4,06	2,38	0,80	2,21	4,58	4,62	1,40	4,40	7,99
	Girls	86	2,39	0,96	2,13	5,05	2,50	0,94	2,21	4,65	4,90	1,82	4,37	9,22
7	**Boys**	83	2,32	0,69	2,08	4,57	2,33	0,59	2,25	3,53	4,65	1,21	4,36	7,58
	Girls	103	2,48	0,99	2,33	4,81	2,52	0,86	2,34	5,10	5,01	1,75	4,59	9,92
8	**Boys**	113	2,73	1,21	2,4	6,49	2,74	1,08	2,54	4,91	5,47	2,22	4,97	10,73
	Girls	113	2,77	0,97	2,54	5,24	2,86	0,89	2,8	5,37	5,63	1,76	5,29	10,47
9	**Boys**	113	2,84	1,06	2,6	5,61	2,81	1,08	2,61	5,55	5,65	2,07	5,26	10,93
	Girls	167	2,78	1,02	2,55	5,34	2,81	0,95	2,6	5,58	2,59	1,85	5,27	10,77
10	**Boys**	118	2,97	0,92	2,85	4,86	2,86	0,77	2,73	4,54	5,83	1,58	5,61	9,12
	Girls	138	3,05	1,04	2,88	5,84	2,98	0,94	2,76	5,83	6,04	1,9	5,71	11,71
11	**Boys**	110	3,31	1,18	3,13	6,42	3,24	1,2	3,07	5,67	6,56	2,23	6,31	11,47
	Girls	130	3,43	1,34	3,14	6,05	3,41	1,1	3,19	5,61	6,84	2,32	6,55	11,52
12	**Boys**	74	3,32	1,02	3,25	5,84	3,28	0,89	3,18	5,71	6,61	1,81	6,35	11,14
	Girls	108	3,7	1,12	3,64	6,07	3,6	1,16	3,39	6,72	7,31	2,1	7,01	12,38
13	**Boys**	81	3,6	1,04	3,62	5,76	3,61	1,02	3,47	5,96	7,22	1,95	7,04	11,56
	Girls	93	4,16	1,4	3,86	7,61	4,01	1,32	3,75	6,41	8,17	2,49	7,92	13,94
14	**Boys**	81	4,11	1,34	3,95	7,49	4,00	1,16	3,82	6,69	8,12	2,36	7,77	13,35
	Girls	105	4,34	1,57	4,10	8,29	4,07	1,32	3,92	6,87	8,41	2,59	8,22	14,44
15	**Boys**	51	4,72	2,03	4,49	10,4	4,49	1,44	4,35	8,03	9,22	3,33	8,79	17,8
	Girls	105	4,6	1,71	4,52	8,54	4,43	1,65	4,2	8,65	9,04	3,18	8,79	16,60
16	**Boys**	60	4,88	2,13	4,73	10,6	4,66	1,8	4,56	9,19	9,55	3,65	8,98	17,99
	Girls	74	4,9	1,73	4,88	8,97	4,51	1,44	4,37	7,65	9,41	3,04	9,33	16,48
17	**Boys**	51	4,86	2,2	4,65	10,67	4,77	1,92	4,61	9,37	9,63	3,95	9,65	19,68
	Girls	55	4,83	1,49	4,72	7,53	4,78	1,91	4,64	10,08	9,61	3,07	9,76	16,20

We observed that the effects of weight, height, TST, SST, BSA, age, and weight on thyroid volume were statistically significant (Sig. (2-tailed)< 0.008) . In the study by Zou Y et al (22), the authors found a statistically significant association in linear regression analysis between thyroid volume and age, gender, BMI, and BSA, as observed in our study. A study by Duatre et al. found that thyroid volume was correlated with age and BSA in boys and girls (23). However, no study has evaluated thyroid volume and skinfold thickness together so far. Based on our results, with other studies, it was seen that thyroid volume can be affected by nutritional status.

In earlier studies about iodine deficiency in different regions of Turkey, goiter prevalence was found to be 6.9% in Konya province, 12.1% in the Agean region (2005), 47.6% in Erzurum province (2004), 1.3% in Ankara province (2009), and 34% in Antalya and Kayseri provinces (24,25). In our previous study, the prevalences of goiter and iodine deficiency prevalence was found to be 17.5 % and 64,2 % in Van province (26). These studies indicated that Turkey is a moderately iodine-deficient country despite decreasing goiter prevalence over time. In addition, regional variations are striking. According to the WHO guidelines, the goiter prevalence was 10.2% in our study. There was a decrease in the goiter prevalence by 7.5 compared with our previous study. Although goiter prevalence was detected by palpation in the first study, the ratios in the studies determining goiter prevalence by simultaneous use of US and palpation suggest that the difference of 7.3% cannot be attributed to differences in the detection technique alone.

Additionally, unlike studies that were conducted on children, we also determined the nodule presence rate in children and determined the nodule prevalence. Nodule prevalence in childhood in the US may range from 0.2% to 5.1% (27). In our country, Ruhuşen Kutlu et al. (24) assessed the prevalence of nodules in children, but only children with nodules at palpation underwent sonographic evaluation. Thus, our study is the first to evaluate nodule prevalence in healthy children in our country.

In our study, the prevalences of goiter and nodules did not differ by sex; however, the results are highly variable in

Table 3. Correlation analysis between thyroid volüme and anthropometric measurements

			Right thyroid lobe (cm_3)				Left thyroid lobe (cm_3)				Total thyroid volume (cm_3)			
BSA (m^2)		**N**	**mean**	**SD**	**median**	**97p**	**mean**	**SD**	**median**	**97p**	**mean**	**SD**	**median**	**97p**
0,7	**Boys**	45	2,08	0,88	1,86	5,84	2,06	0,71	1,89	5,03	3,98	0,90	3,79	6,88
	Girls	72	1,93	0,58	1,87	2,89	2,06	0,76	2,03	3,38	4,00	1,27	3,85	5,99
0.8	**Boys**	115	2,25	0,58	2,12	3,53	2,35	0,57	2,32	3,54	4,61	0,98	4,39	7,01
	Girls	150	2,24	0,57	2,14	3,59	2,32	0,52	2,21	3,53	4,57	1,00	4,42	7,01
0.9	**Boys**	154	2,41	0,61	2,36	3,63	2,47	0,61	2,39	4,07	4,89	1,10	4,84	7,46
	Girls	158	2,45	0,60	2,39	4,03	2,49	0,57	2,44	3,82	4,95	1,04	4,81	7,32
1.0	**Boys**	158	2,67	0,59	2,65	4,26	2,72	0,65	2,62	4,06	5,39	1,14	5,26	8,15
	Girls	144	2,77	0,87	2,61	5,25	2,82	0,72	2,72	4,69	5,60	1,47	5,44	9,95
1.1	**Boys**	112	2,89	0,73	2,84	4,44	2,93	0,61	2,88	4,18	5,82*	1,21	5,76	8,54
	Girls	112	3,04	0,65	2,95	4,57	3,09	0,68	2,98	4,63	6,14	1,11	6,11	8,62
1.2	**Boys**	82	3,40	0,84	3,38	5,37	3,32	0,84	3,36	5,49	6,73	1,57	6,75	10,06
	Girls	106	3,48	0,86	3,38	5,57	3,31	0,87	3,14	5,58	6,80	1,61	6,37	10,88
1.3	**Boys**	66	3,70	0,87	3,62	5,97	3,51*	0,84	3,47	4,95	7,22	1,50	6,81	11,05
	Girls	113	3,86	1,02	3,68	5,80	3,95	1,26	3,75	6,14	7,81	2,02	7,23	12,15
1.4	**Boys**	62	3,84	0,87	3,64£	6,22	3,74	0,88	3,57£	6,04	7,58	1,56	7,18£	12,26
	Girls	183	4,56	1,38	4,23	7,88	4,34	1,32	4,01	7,41	8,90	2,50	8,31	15,26
1.5	**Boys**	62	4,61	1,25	4,24*	7,80	4,21	1,17	4,07¥	6,80	8,82	2,17	8,07¥	13,76
	Girls	140	5,02	1,37	4,94	8,00	4,59	1,17	4,50	7,19	9,61	2,26	9,30	15,83
1.6	**Boys**	72	5,23	1,44	4,97	8,86	5,03	1,37	4,93	8,81	10,27	2,61	10,01	17,71
	Girls	75	5,29	1,67	4,94	8,77	5,00	1,60	4,82	8,74	10,30	2,93	9,97	15,55
1.7	**Boys**	78	6,15	2,19	5,58	12,42	5,74	1,65	5,60	9,49	11,89	3,56	11,19	20,54
	Girls	25	5,12	1,64	4,98	8,98	4,99	1,64	4,94	7,96	10,11	3,11	9,65	16,50

*:p<0,05; ¥:<0,01; £: p<0,001, superscript letters indicate the comparison of each parameter in each BSA group about gender.

Table 4. Range, mean, median, and standard deviation of the thyroid gland volume for BSA

Variable	Right TLV Correlation	Left TLV Correlation	TTV Correlation
Age	0.565	0.548	0.580
Gender	0.058	0.055	0.059
BSA	0.788	0.760	0.807
BMI	0.789	0.763	0.809
Height	0.770	0.741	0.787
Weight	0.789	0.763	0.809
Waist c.	0.672	0.648	0.688
Hip c.	0.764	0.737	0.783
TST	0.258	0.243	0.261
SST	0.419	0.407	0.432

SST: Subscapular skin thickness; TST: Triceps skin thickness; C: Circumference; BMI: Body mass index; BSA: Body surface area; TLV: thyroid lobe volume, B. Boys, G: Girls, TLV: Thyroid lobe volume; TTV: Total thyroid volume

studies evaluating the relationship between goiter prevalence and sex (8,24,28). In our study, no reasonable explanation could be made for the higher prevalence of goiter in girls aged 6-9 years.

In many studies, no association between thyroid volume and urinary iodine deficiency was observed (29,30). On the other hand, thyroid volume can change according to sex, BSA, age, and ethnic origin (24-27). However, a limited number of studies have determined the upper limits of the thyroid gland when evaluating thyroid volume in children in Turkey. The thyroid volumes of our children were greater than those presented by the World Health Organization (16). In the present study, we would determine the degree of ID more accurately and could use the values obtained as normal reference values for assessments of thyroid volume in children without ID by stratifying children with or without ID if we were able to use UIE in addition to thyroid sonography. Nevertheless, we think that reference values in our study can be helpful until more ideal percentile curves are created, as iodine deficiency is still endemic in our country.

Limitations

1. The study was conducted in a single region.
2. There is a possibility that differences in personal experience may become prominent during radiological evaluations.

Table 5. Comparison of the frequency of goiter and nodule presence according to sex and age

Yaş	Boys Goiter (n %)	Boys' nodula (n %)	Boys' long axis of the nodule (mm)	Girls Goiter (n %)	Girls Nodula (n %)	Girls Long axis of the nodule (mm)
6	13 (18.6)*	0 (0)**	-	28 (32.6)	1 (1.2)	7.5
7	16 (19.3)**	0 (0)**	-	22 (21.4)	0 (0)	-
8	24 (21.2)**	1 (0.9)**	10	17 (15)	0 (0)	-
9	19 (16.8)*	0 (0)**	-	15 (9.0)	0 (0)	-
10	13 (11)**	1 (0.8)**	6	7 (5.1)	2 (1.4)	6, 4
11	11 (10)**	1 (0.9)**	5	13 (10)	1 (0.8)	9
12	5 (6.8)**	0 (0)**	-	4 (3.7)	0 (0)	-
13	1 (1.2)***	0 (0)**	-	4 (4.3)	0 (0)	-
14	2 (2.5)**	0 (0)**	-	3 (2.9)	1 (1)	6
15	1 (2.0)**	1 (2.0)**	11	4 (3.8)	4 (3.8)	5.5, 6, 7, 7
16	5 (8.2)**	1 (1.6)**	7	2 (2.7)	3 (4.1)	5, 6, 6
17	3 (5.9)**	1 (2.0)**	5	1 (1.8)	1 (1.8)	14
Total	117 (11.3)**	7 (0.7)**	-	120 (9.4)	13 (1)	-

Significant at 5% level, ** Significant at 1% level, *** Significant at 0.1% level*: superscripted letters show p values obtained from the comparison of the frequency of goiter and nodule presence between genders.

Table 6. Comparison of the frequency of goiter according to sex and BSA

BSA	Boys Goiter (n %)	Girls Goiter (n %)
0.8	44 (38.3)**	53 (35.3)
0.9	46 (29.9) ¥	25 (15.8)
1	39 (24.7) £	11 (7.6)
1.1	17 (15.2) ¥	5 (4.5)
1.2	15 (18.3) ¥	5 (4.7)
1.3	8 (12.1) **	9 (8)
1.4	3 (4.9)**	21 (11.5)
1.5	5 (8.1)**	10 (7.1)
1.6	4 (5.6)**	7 (9.3)
1.7	11 (14.1)**	1(4.5)
Total	192 (19.1) £	147 (11.5)

** Significant at 1% level (¥ Boys, £ Girls)
p<0,001; *: p<0,05; **: p>0,05, superscripts letter shows p values obtained from the comparison of the frequency of goiter and nodule presence between genders.

CONCLUSION

Thyroid volume was influenced by age, weight, subcutaneous tissue thickness, waist circumference, and body surface area (BSA). Goiter remains a significant public health concern among school-aged children in Van Province. Furthermore, it is important to emphasize the need for additional studies to establish reference values for normal thyroid volume in children with adequate iodine levels. This study was limited to a single region; thus, it should be supported by larger, multicentric studies encompassing diverse regions.

Ethics Committee Approval: This study was approved by the Ethical Committee of Van Yüzüncü Yıl University (Decision No: 25, Date: 05.09.2013).

Informed Consent: Written consent was obtained from the participants.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- S.K., M.D., A.Y.; Data Acquisition- S.K., M.D., A.Y.; Data Analysis/Interpretation- S.K., M.D., A.Y., S.K.; Drafting Manuscript- S.K., M.D., A.Y., S.K.; Critical Revision of Manuscript- S.K., S.K.; Final Approval and Accountability- S.K., M.D., A.Y., S.K.

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REFERENCES

1. Andersson M, Braegger CP. The Role of Iodine for Thyroid Function in Lactating Women and Infants. Endocr Rev. 2022;43(3):469-506. doi:10.1210/endrev/bnab029
2. Manousou S, Dahl L, Heinsbaek Thuesen B, Hulthén L, Nyström Filipsson H. Iodine deficiency and nutrition in Scandinavia. Minerva Med. 2017;108(2):147-158. doi:10.23736/S0026-4806.16.04849-7
3. Köhrle J. Selenium, Iodine and Iron-Essential Trace Elements for Thyroid Hormone Synthesis and Metabolism. Int J Mol Sci. 2023;24(4):3393. Published 2023 Feb 8. doi:10.3390/ijms24043393
4. Chávez Valencia V, Mejía Rodríguez O, Viveros Sandoval ME, et al. Prevalence of malnutrition-inflammation complex syndrome and its correlation with thyroid hormones in chronic haemodialysis

patients. Prevalencia del síndrome complejo de malnutrición e inflamación y su correlación con las hormonas tiroideas en pacientes en hemodiálisis crónica. Nefrologia (Engl Ed). 2018;38(1):57-63. doi:10.1016/j.nefro.2017.07.001

5. Ersoy B, Günes HS, Gunay T, Yilmaz O, Kasirga E, et al. .Interaction of two public health problems in Turkish schoolchildren: nutritional deficiencies and goitre. Public Health Nutr. 2006 Dec;9(8):1001-6.
6. Korobitsyna R, Aksenov A, Sorokina T, Trofimova A, Grjibovski AM. Iodine Status of 6-12-Year-Old Children in Russia over the Past 10 Years: A Scoping Review. Nutrients. 2022;14(4):897. Published 2022 Feb 21. doi:10.3390/nu14040897
7. Köse Aktaş A, Gökçay Canpolat A, Aydin Ü, et al. Intensifying Iodine Deficiency Throughout Trimesters of Pregnancy in a Borderline Iodine-Sufficient Urban Area, Ankara, Turkey. Biol Trace Elem Res. 2022;200(6):2667-2672. doi:10.1007/s12011-021-02903-y
8. Anaforoğlu İ, Algün E, İnceçayır Ö, Topbaş M, Erdoğan MF. Iodine status among pregnant women after mandatory salt iodisation. Br J Nutr. 2016;115(3):405-410. doi:10.1017/S0007114515004559
9. Bauer AJ, Francis GL. Evaluation and management of thyroid nodules in children. Curr Opin Pediatr. 2016;28(4):536-544. doi:10.1097/MOP.0000000000000364
10. Fryar CD, Gu Q, Ogden CL, Flegal KM. Anthropometric Reference Data for Children and Adults: United States, 2011-2014. Vital Health Stat 3 Anal Stud. 2016;(39):1-46.
11. Looney DP, Potter AW, Arcidiacono DM, Santee WR, Friedl KE. Body surface area equations for physically active men and women. Am J Hum Biol. 2023;35(2):e23823. doi:10.1002/ajhb.23823
12. Lee EY, Yoon KH. Epidemic obesity in children and adolescents: risk factors and prevention. Front Med. 2018;12(6):658-666. doi:10.1007/s11684-018-0640-1
13. Bravo G, Bragança S, Arezes PM, Molenbroek JFM, Castellucci HI. A literature review of anthropometric studies of school students for ergonomics purposes: Are accuracy, precision and reliability being considered?. Work. 2018;60(1):3-17. doi:10.3233/WOR-182719
14. Peterson S., Sanga A, Eklöf H, Bunga B, Taube A, et el. Classification of thyroid size by palpation and ultrasonography in field surveys. Lancet 2000; 355:106-10.
15. Lee YJ, Choi YH, Lim YH, et al. Effects of iodine status on thyroid volume and goiter in children living in an iodine-replete area. Eur Thyroid J. 2023;12(6):e230219. Published 2023 Dec 18. doi:10.1530/ETJ-23-0219
16. 41. DE Maeyer EM, Lowenstein FW, Thilly CH. The control of endemic goitre. WHO Publ, Genava, 1995.
17. Grani G, Sponziello M, Pecce V, Ramundo V, Durante C. Contemporary Thyroid Nodule Evaluation and Management. J Clin Endocrinol Metab. 2020;105(9):2869-2883. doi:10.1210/clinem/dgaa322
18. Johnson A, Edwards C, Reddan T. A review of sonographic thyroid volume and iodine sufficiency in children: An Australian perspective. Australas J Ultrasound Med. 2019;23(1):33-38. Published 2019 Nov 1. doi:10.1002/ajum.12189
19. Wang N, Fang H, Fu C, et al. Associations of adiposity measurements with thyroid nodules in Chinese children living in iodine-sufficient areas: an observational study. BMJ Open. 2017;7(10):e016706. Published 2017 Oct 30. doi:10.1136/bmjopen-2017-016706
20. Bayram F, Borazan B, Torun E, Tanrıverdi F., Güven M., et al. The Prevalence of Endemic Goiter and Iodine Deficiency and Evaluation of Thyroid Functions in an Area of Central Anatolia, Turk J Endocrinol Metab 2003;1:37-43
21. Xiao Y, Mao J, Mao X, et al. Metabolic syndrome and its components are associated with thyroid volume in adolescents. BMC Endocr Disord. 2021;21(1):176. Published 2021 Aug 28. doi:10.1186/s12902-021-00833-3
22. Guo W, Tan L, Dong S, et al. New Reference Values for Thyroid Volume and a Comprehensive Assessment for Influencing Factors in Chinese Adults with Iodine Sufficiency. Eur Thyroid J. 2021;10(6):447-454. doi:10.1159/000513494
23. Duarte GC, Tomimori EK, de Camargo RY, Catarino RM, Ferreira JE, Knobel M, Medeiros-Neto G.Excessive iodine intake and ultrasonographic thyroid abnormalities in schoolchildren. .. J Pediatr Endocrinol Metab. 2009 Apr;22(4):327-34.
24. Kutlu R, Karaköse S, Güngör K, Kulaksizoğlu S. The goiter prevalence and urinary iodine levels among adolescents. *Turk J Pediatr*. 2011;53(2):161-168.
25. Kurtoglu S, Covut IE, Kendirci M, Uzum K, Durak AC, et al. Normal thyroid volume of children in Turkey: Pilot study in Kayseri province. IDD Newsletter 1995; 11:41-42.
26. Doğan M, Acikgoz E, Acikgoz M, Cesur Y, Ariyuca S, Bektas MS. The frequency of Hashimoto thyroiditis in children and the relationship between urinary iodine level and Hashimoto thyroiditis. J Pediatr Endocrinol Metab. 2011;24(1-2):75-80. doi:10.1515/jpem.2011.115.
27. Sandy JL, Titmuss A, Hameed S, Cho YH, Sandler G, Benitez-Aguirre P. Thyroid nodules in children and adolescents: Investigation and management. J Paediatr Child Health. 2022;58(12):2163-2168. doi:10.1111/jpc.16257
28. Lin Z, Lu C, Teng D, et al. Influencing Factors and New Reference Intervals of Adult Thyroid Volume in Iodine-Sufficient Areas of China. Biol Trace Elem Res. 2023;201(12):5652-5661. doi:10.1007/s12011-023-03635-x
29. Angermayr L, Clar C. WITHDRAWN: Iodine supplementation for preventing iodine deficiency disorders in children. Cochrane Database Syst Rev. 2018;11(11):CD003819. Published 2018 Nov 29. doi:10.1002/14651858.CD003819.pub3
30. Chen W, Li X, Wu Y, et al. Associations between iodine intake, thyroid volume, and goiter rate in school-aged Chinese children from areas with high iodine drinking water concentrations. Am J Clin Nutr. 2017;105(1):228-233. doi:10.3945/ajcn.116.139725

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RESEARCH ARTICLE

Metabolic Syndrome and Type 2 Diabetes Mellitus in Overweight and Obese Children: A Single Centre Experience

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ABSTRACT

Objective: Childhood obesity is associated with various risks, including insulin resistance, type 2 diabetes mellitus (DM), hypertension, and metabolic syndrome (MetS). This study evaluated MetS and type 2 diabetes mellitus (DM) in overweight and obese children.
Methods: Between 2000 and 2013, 474 obese and overweight children aged <18 years were included in this study. The clinical characteristics of the patients with MetS and type 2 DM were evaluated.
Results: Of the patients, 50.4% (n = 239) were girls, and the mean age was 10.91±3.06 years. According to the body mass index, 20.5% (n=97) of the patients were overweight and 79.5% (n=377) were obese. Blood pressure, striae, and acanthosis nigricans were significantly higher in the obese group than in the overweight group (p <0.05). MetS was found in 30.8% (n=146) of the patients. The MetS rate was 37.7% (n=142) in the obese patients and 4.1% (n=4) in the overweight patients, and the difference between them was statistically significant (p<0.001) Based on the oral glucose tolerance test; 45 (9.5%) patients had impaired fasting glycaemia, 24 (5%) had impaired glucose tolerance and 4 (0.84%) had type 2 DM. One patient with normal glucose balance at admission, who was diagnosed with type 2 DM in the 4th year, was overweight and had a family history of diabetes, hyperinsulinemia, and high HOMA-IR.
Conclusions: The results of our study showed that both obese and overweight children are at risk of developing MetS and type 2 DM, particularly in the presence of risk factors. Close monitoring of these children is important to prevent complications.

Keywords: Childhood obesity, overweight, metabolic syndrome, type 2 diabetes mellitus

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INTRODUCTION

Obesity is defined by the World Health Organisation (WHO) as the unusual or excessive buildup of body fat tissue to the extent that it impairs health. Obesity, caused by genetic, environmental, metabolic, and hormonal factors, is a metabolic condition that can result in social, psychological, and medical complications (1). As 40 million children under the age of five were overweight as of 2011, the WHO prepared a global strategy plan to prevent and control obesity in the period 2008-2013, but by 2020, a total of 39 million children <5 years of age and 340 million children and adolescents between the ages of 5 and 19 years are obese or overweight.

The prevalence of obesity varies among countries. In the UK, an increase from 9.9% to 14.4% among 4-5 year olds and from 21% to 25.5% among 6 year olds was observed when comparing 2019/20 and 2020/21 school children (2). In Egypt, approximately one in six (17%) of 42,568 children under 5 years of age were overweight or obese. Severe obesity in children also increased 1.7-fold in a study comparing 2006-2017 and 1967-2007 (3). According to the Turkey Demographic and Health Surveys (TDHS), the rate of overweight increased from 5.3% in 1998 to 11.6% in 2013 (4). In a study in Turkey, 14.3% of children aged 6-10 were overweight and 6.5% were obese (5). In 2016, 9.9% of 7-8 year-olds were overweight and 14.6% were obese; in 2017, 19.5% of 10-14 year-olds were overweight and 10.5% were obese, and 15% and 5.6% of 15-18 year-olds were obese (6,7).

Childhood obesity is associated with various risks, including insulin resistance, type 2 diabetes mellitus (DM), hypertension, fatty liver disease, metabolic syndrome (MetS), and subclinical atherosclerosis, in early adulthood (1,8-11). Although there is no clear international definition of MetS for children and adolescents, obesity is an important cardiovascular risk factor associated with other metabolic problems. Considering that obesity is also an important risk factor for the development of type 2 diabetes and possible complications of MetS in children, the prevention of obesity at an early age is important in terms of complications that may develop and ensure a healthy adult life (12,13). In this study, we aimed to assess the prevalence of MetS and type 2 DM among overweight and obese children and identify the risk factors associated with these conditions. Additionally, we highlighted the shifts in the glucose balance that occurred during follow-up.

MATERIALS AND METHODS

Participant

This retrospective cohort study included 474 patients aged <18 years who were referred to the Department of Paediatric Endocrinology, Istanbul University Faculty of Medicine, between 2000 and 2013 with complaints of overweight and obesity. Patients with diseases, those taking medications that may affect body weight, or those with genetic syndromes were excluded. The demographic, physical examination, and laboratory data of the patients were retrospectively evaluated by analysing their medical records at admission, 6 months, and annually.

Definitions

According to Body Mass Index (BMI), overweight was defined 85-95 p (+1 and +2 SDS), and obesity was defined as >95 percentile (>+2 SDS). The WHO Health Organisation criteria adapted for children were used to define MetS (8). According to the defined criteria, patients with and without MetS in the patient population were compared in terms of demographic characteristics, physical examination results, and laboratory findings.

Definition of MetS (8)**;**

Three or more of the following;

- BMI> 95th p
- Abnormal glucose homoeostasis: Any of the following; a- fasting hyperinsulinemia; b- impaired fasting glucose; c- impaired glucose tolerance
- Hypertension: Systolic blood pressure (BP)> 95th p
- Dyslipidemia: Any of the following; a- high triglycerides [>105 mg/dL, <10 y; 136 mg/dL 10 y]; b- low HDL-cholesterol <35 mg/dL; c- high total cholesterol >(95th p)

Hyperinsulinism was defined based on the puberty stage. Impaired fasting glycaemia (IFG), Impaired Glucose Tolerance (IGT), and type 2 DM were defined according to the American Diabetes Association criteria (ADA) (8,14).

Abnormal glucose homoeostasis;

• Hyperinsulinism	Prepubertal> 15 mU/L Post-pubertal >20 mU/L
• IFG	Fasting plasma glucose (FPG) 100-126 mg/dL
• IGT	2nd hour glucose 140-199 mg/dL on the oral glucose tolerance test (OGTT).
• Type 2 DM	FGF > 126 mg/dL or 2nd hour plasma glucose 200 mg/dL on OGTT or plasma glucose level (random) 200 mg/dL or HbA1C >6.5%

HOMA-IR (homeostasis model assessment for insulin resistance: FPG (mg/dL)×fasting insulin level (µU/ml) /405) limit values above 2.16 and 5.2 in prepubertal/pubertal boys and above 2.22 and 3.83 in prepubertal/pubertal girls have been defined as insulin resistance (15).

The obese and overweight groups were compared in terms of demographic characteristics, physical examination results, laboratory results, frequency of metabolic syndrome, and differences in abnormal glucose balance.

Ethics committee

This study was approved by the Ethics Committee of Istanbul University, Faculty of Medicine on 02.10.2013 (File No:2013/1245). This article is based on my thesis entitled "Prevalence of Metabolic Syndrome and Type 2 Diabetes in Children with Exogenous Obesity", which was conducted under the supervision of Rüveyde Bundak at Istanbul University in 2014.

Statistical analysis

Statistical data were analysed using SPSS version 15 (SPSS Inc, Chicago, IL, USA). In addition to descriptive statistical methods (mean, standard deviation, etc.), the chi-square test and Fisher's exact test were used for categorical variables, and the Student's T-test and Mann-Whitney U test were used to compare means between the two groups. The results were evaluated at a 95% confidence interval (CI), and significance was set at $p<0.05$.

RESULTS

In total, 474 obese and overweight patients were included in this study. Of the patients, 50.4% (n:239) were girls and the mean age at presentation was 10.91±3.06 (0.90-17.20) years. The mean age of girls was 10.86±3.12 (0.9-17.5) years and the mean age of boys was 10.97±3.00 (1.25-17.2) years, and there was no statistically significant difference between them in terms of age. According to birth weight for gestational age; 88,6% (n=420) were appropriate for gestational age (AGA), 10.5% (n=50) were large for gestational age (LGA) and 0,84%(n=4) were small for gestational age.

Comparison of the obese and overweight groups

According to the BMI, 20.5% (n=97) of the patients were overweight and 79.5% (n=377) were obese. In the obese group, age was significantly younger (p=0.008), birth length was longer (p=0.041), and paternal weight was higher (p=0.033) than in the overweight group. The blood pressure percentiles (p=0.027), striae (p=0.002), and acanthosis nigricans (p=0.005) were significantly higher in the obese group. The FPG levels were significantly lower in the overweight group than in the obese group (p=0.027). There were no statistically significant differences between the other characteristics, physical examination results, and laboratory findings (Table 1).

Metabolic syndrome

MetS was found in 30.8% (n = 146) of the patients. The MetS rate was 37.7% (n = 142) in the obese patients and 4.1% (n = 4) in the overweight patients, and the difference between the two groups was statistically significant (p = 0.0001). Among the patients with MetS, 52.7% (n = 77) were girls, and the mean age was 11.30±2.82 (4.6-16.5) years. The incidence of heart disease in the family was significantly higher (p=0.014) in the MetS group; however, there were no statistically significant differences in terms of other parameters (Table 2).

Among the patients, 71.4% (n = 100) had dyslipidemia, 23.7% (n = 33) had high cholesterol, 55.7% (n = 78) had high triglycerides, 19.8% (n = 26) had low HDL cholesterol, 61.6% (n =90) had BP > 97p, 97.3% (n = 142) had BMI >95p, 91.1% (n = 133) had hyperinsulinemia, and 83.2% (n = 109) had high HOMA-IR levels (Figure 1).

Table 1. Family/medical history and laboratory parameters in obese and overweight children (mean±SD or N/%)

	Obese	Overweight	P
Age (year)	10.75±3.18	11.54±2.43	**0,008**
Sex Girl	198 (52.5)	41 (42.3)	0.072
Boy	179 (47.5)	56 (57.7)	
Birth weight (gr)	3429.10±640.5	3464.79±543.3	0.058
Birth height (cm)	50.83±2.5	49.91±3.0	**0,041**
Prematurity	24 (6.4)	4 (4.2)	0.403
CS	165 (45)	37 (37.4)	0.329
Maternal BMI (kg/m2)	31.63±9.8	32.50±9.05	0.389
Paternal BMI (kg/m2)	32.78±14.1	29.37±4.7	0.295
Paternal weight (kg)	93.6±17.04	85.19±13.5	**0.033**
Family history			
Obesity	205 (54.8)	47 (48.5)	0.263
Type 2 DM	133 (35.6)	37 (38.1)	0.637
Hypertension	62 (16.6)	14 (14.4)	0.602
Heart disease	19 (5.1)	3 (3.1)	0.590
Hyperlipidaemia	15(4)	8 (8.2)	0.109
Physical examination			
Acanthosis nigricans	72 (19.1)	7(7.2)	**0.005**
Striae	73 (19.4)	6(6.2)	**0.002**
BP >95 percentile	122 (32.4)	20(20.8)	**0.027**
Pubertal	188 (49.9)	41(42.3)	0.624
Prepubertal	189 (50.1)	56(57.7)	
Laboratory			
FPG (mg/dL)	90.30±10.7	84.40±14.62	**0.027**
Hyperinsulinemia	212 (59.4)	47 (52.2)	0.216
High HOMA-IR	193 (60.1)	34 (44.7)	**0.015**
High Cholesterol	47 (13.6)	17 (19.8)	0.152
HDL-cholesterol	48.39±16.2	54.45±14.4	**<0.001**
LDL- cholesterol	95.95±31.09	101.08±34.82	0.326
Hypertriglyceridaemia	120 (34.6)	22 (26.2)	0.142
Hepatosteatosis	47 (12.8)	8(8.2)	0.514

NSVD: normal spontaneous vaginal delivery, CS: Caesarean section, DM: diabetes mellitus, BMI: body mass index SDS: standard deviation score NS: non-significant, BP: blood pressure, FPG: fasting plasma glucose

Table 2. Comparison of family medical history and physical examination between the groups in MetS+/- (mean±SD or N/%)

	MetS+	MetS-	p
Age (year)	11.03±2.91	10.85±3.13	0.544
Sex Girl	77 (52.7)	162 (49.4)	0.501
Boy	69 (47.3)	166 (50.6)	
Birth weight (gr)	3403.82±632.74	3452.9±614.91	0.442
Birth height (cm)	50.76±2.61	50.55±2.7	0.570
Prematurity	9 (6.3)	19 (5.8)	0.865
CS	60 (42.6)	142 (44.4)	0.716
Maternal BMI (kg/m2)	32.09±9.5	31.66±9.8	0.820
Paternal BMI (kg/m2)	30.49±6.4	32.83±14.99	0.339
Gestational DM	2 (1.4)	6 (1.9)	0.999
Family history			
Obesity	81 (55.5)	171 (52.6)	0.564
Type 2 DM	55 (37.7)	115 (35.4)	0.633
Hypertension	29 (19.9)	47 (14.5)	0.144
Heart disease	12 (8.2)	10 (3.1)	**0.014**
Hyperlipidaemia	8 (5.5)	15 (4.6)	0.687
Physical examination			
BMI SDS	2.49±0.76	2.49±0.76	**<0.001**
BP>95 percentile	53 (16.2)	53 (16.2)	**<0.001**
Acanthosis nigricans	47 (14.3)	47 (14.3)	**0.041**
Striae	45(13.7)	45(13.7)	**0.010**

BP: blood pressure, BMI: body mass index, SDS: standard deviation score, CS: Caesarean section, DM: diabetes mellitus

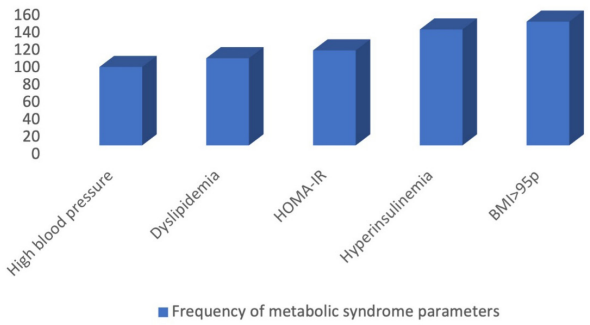

Figure 1: Frequency of metabolic syndrome parameters

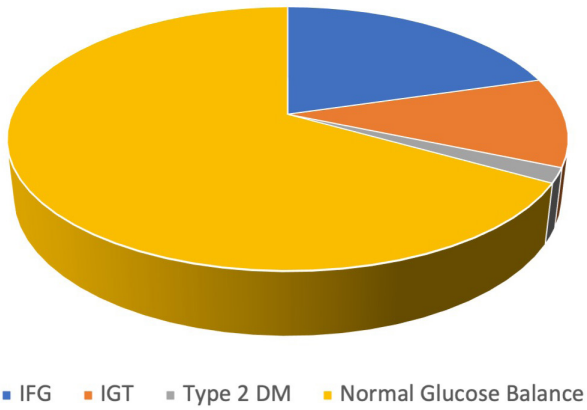

Figure 2: Distribution of glucose homeostasis

Comparison of physical examination and laboratory parameters between the MetS and non-MetS groups

Physical examination and laboratory parameters of the two groups at admission at 6th month, 1st year and 2nd year were compared (Table 3). BMI SDS, BP >95p, acanthosis, striae, FPG, HOMA-IR, insulin, total cholesterol, triglycerides, and LDL-cholesterol were significantly higher in the MetS group. In the 6th month of follow-up, BMI, SDS, and total cholesterol were significantly higher, and HLD-cholesterol was significantly lower in the MetS group. In the 1st year, BMI SDS, LDL-cholesterol, and HOMA-IR were statistically significantly higher in the MetS group.

Type 2 DM

OGTT was performed in 220 patients at the first presentation. According to the OGTT and FPG results, 45 (9.5%) patients had IFG, 24 (5%) had IGT, and four (0.84%) had type 2 DM (Figure 2).

IFG-IGT-type 2 DM was found in the obese (8.4%-6.3%-0.8%) and overweight (15.2%-1.1%-1.1%) groups, with no statistically significant difference between the two groups. In the patients who had type 2 DM, it was observed that two patients had a family history of type 2 DM and one patient had a history of low birth weight.

The incidences of IFG and IGT were significantly higher in the MetS group (11.7% and 11%, respectively) than in the non-MetS group (8.9% and 2.5%) (p<0.001).

Changes in glucose balance during follow-up

Among patients with normal glucose balance at admission (n = 387), IGT was found in three patients in the 2nd year, one

Table 3. Comparison of physical examination and laboratory parameters between the groups in MetS+/- (mean± SD or n/%)

	First examination			6th month			1st year		
	MetS+	MetS-	p	MetS+	MetS-	p	MetS+	MetS-	p
BMI SDS	2.86±0.7	2.49±0.76	**<0.001**	2.59±0.70	2.32±0.75	**0.001**	2.62±0.8	2.32±0.83	**0.017**
BP>95 percentile	90 (61)	53 (16.2)	**<0.001**	14 (38.9)	22 (6.7)	0.059	12(42.9)	27 (8.2)	0.064
Acanthosis nigricans	32 (21.9)	47 (14.3)	**0.041**	10(17.9)	14(4.3)	0.623	6(12.2)	16(4.9)	0.702
Striae	34 (23.3)	45(13.7)	**0.01**	10(17.9)	12 (3.7)	0.075	5(10.2)	15(4.6)	0.563
FPG (mg/dL)	93.1±11.2	89.89±10.1	**0.047**	91.97±8.95	91.85±7.9	0.403	88.86±12.4	88.89±11.8	0.673
Insulin (µU/ML)	26.6±12.04	17.4±13.4	**<0.001**	20.6±11.64	17.18±11.9	0.455	25.9±26.07	18.46±13.3	0.901
HOMA-IR	5.79±3.12	3.87±2.97	**<0.001**	4.63±2.52	3.86±2.72	0.067	6.15±7.2	4.31±3.4	0.045
Total-c (mg/dL)	175.8±37.7	168±78.3	**0.002**	164.55±26.8	168.48±39.4	0.681	180.79±35.62	167.13±32.1	0.367
Triglycerides (mg/dL)	139.7±67.6	103.95±54.8	**<0.001**	147.7±84.4	106.9±58.1	**0.026**	127.09±58	109.6±56.3	0.098
HDL-c (mg/dL)	45±11.1	50.9±13.2	**<0.001**	42.15±8.7	52.3±14.3	**0.02**	44.58±9.03	51.2±16.7	0.061
LDL-c (mg/dL)	103.34±36.4	95±29.7	**0.034**	98.45±32.4	92.52±33.46	0.516	106.96±26.4	93.2±26.02	**0.027**

c:cholesterol, FPG: fasting plasma glucose, BP: blood pressure, BMI: body mass index, SDS: standard deviation score

patient in the 3rd year, type 2 DM in two patients, and IFG in one patient in the 4th year (Table 4).

The patient diagnosed with type 2 DM in the 4th year was overweight and had a family history of diabetes, hyperinsulinemia, high HOMA-IR, and Polycystic Ovary Syndrome.

Table 4. IFG/IGT/Type 2 DM during follow-up (N/%)

	Type 2 DM	IGT	IFG	NGB	Total (n)
First examination	4 (0.84)	24 (5.06)	45 (9.5)	401 (84.6)	474
6**th** month	-	1 (0.9)	-	114 (99.1)	115
1**st** year	1 (0.8)	4 (3.2)	3 (2.4)	116 (93.5)	124
2**nd** year	1 (1.1)	3 (3.3)*	2 (2.2)	84 (93.3)	90
3**th** year	-	1 (1.5)*	1 (1.5)	63 (96.9)	65
4**th** year	1 (1.9)*	-	2 (3.9)*	48 (94.1)	51

IGT: Impaired glucose tolerance, IFG: Impaired fasting glucose, NGB: Normal glucose balance, DM: Diabetes Mellitus**,** * newly diagnosed patients

DISCUSSION

In this study, the prevalence of MetS was 30.8%, and it was shown to occur not only in obese individuals but also in overweight individuals. Type 2 DM has also been reported to develop during follow-up in the presence of risk factors.

The prevalence of MetS varies according to the criteria used and from community to community. Attempts have been made to modify and adapt the criteria used by adults for children. However, because blood pressure, lipid levels, and insulin levels change with puberty and age in children, there are problems with this definition. In a study of children aged 6-18 years, the prevalence of MetS in children aged 10 years was 14.3%-3.7% in obese and overweight children according to the International Diabetes Federation (IDF) 2007 criteria and 32.3%-8.4%; according to The National Cholesterol Education Programme's Adult Treatment Panel III (NCEP ATP) criteria. The prevalence of MetS in children aged less than 10 years was higher in the obese than in the overweight (16). Waist circumference, glucose, triglycerides, insulin, and HOMA-IR levels were higher and high-density lipoprotein (HDL) cholesterol levels were lower in the obese group than in the normal weight group. Between the ages of 10-18 years, 8.1% of the children were overweight, 9.2% were obese, 4.4% had MetS, and 43.9% had at least one component of MetS (17). The prevalence of MetS was found to be 28.7% by Cook et al., 38.7% by Weiss et al., and 38.7% by De Ferranti 10% and has been reported to increase 3-5-fold during puberty (18-20). In a study in Turkey, MetS was significantly more common in obese children than in overweight children and significantly more common in adolescents than in preadolescents (21). We also found that it was significantly higher in obese patients; however, no significant difference was observed in terms of puberty. In different studies in our country, the MetS rate was found to be 39%, 56.4%, and 38.8% according to the modified

WHO criteria (22-24) and a 1-point increase in BMI doubled the prevalence of MetS by two times (25).

A meta-analysis showed that the risk in children increased with the presence of MetS in parents (26). Children with a family history of diabetes and/or hypertension have a 4.7 times higher risk for MetS than those without a family history (27). In our study, the prevalence of heart disease in the family was found to be statistically significantly higher in the MetS group.

Acanthosis nigricans and striae are the manifestations of MetS. Acanthosis nigricans is used in the clinical evaluation of laboratory-proven insulin resistance, and the risk of type 2 diabetes is increased in those who are positive (28).

Children affected by obesity due to acanthosis nigricans were twice as likely to develop MetS after adjusting for sex, ethnicity, and strata (29). Additionally, serum insulin and HOMA-IR levels, which are parameters of MetS, were higher in obese children with acanthosis nigricans (30). We also found that the incidence of acanthosis nigricans was significantly higher in both the obese and MetS groups.

There is no consensus on the cutoff value for HOMA-IR in children. In a cohort study investigating metabolic proliferation and insulin resistance at the age of 6 years, when HOMA-IR ≥1.93, insulin resistance was significantly higher in obese/overweight children and 26% had at least one risk factor for MetS (31). In our study, HOMA-IR and FPG levels were significantly higher in obese children than in overweight children and in children with MetS than in those without MetS. The incidence of IFG-IGT was significantly higher in the MetS group (11.7% -11%) than in the non-MetS group (8.9%-2.5%). Insulin resistance is a known risk factor in later stages; although it can be reversible in the early stages, it can cause irreversible damage if left untreated. Morrison et al. found that 10-year-old girls diagnosed with both MetS and hyperinsulinemia had a higher frequency of progression to type 2 DM, 14 years later (32). Although many factors contribute to the development of type 2 DM, in a meta-analysis, the prevalence of type 2 DM in children was 75.27%, and obesity was found to be an important risk factor (33). The intermediate stages in the progression from normal glucose tolerance to type 2 DM include impaired fasting glucose and glucose tolerance. The factors-underlying the development of an abnormal glucose balance are multifactorial. In a multicenter study, the prevalence of IFG and IGT in obese children was 15.2%, hyperinsulinism was 57.1%, and 25% of children with type 2 DM had a family history of type 2 DM (34). A study found a high conversion rate of 27% from IGT to type 2 DM within an average of 1.7 years and 10% from normal glucose tolerance to type 2 DM within 2.5 years after the detection of abnormal glucose metabolism in obese adolescents, which was associated with BMI, severity of insulin resistance, and presence of non-alcoholic fatty liver disease (NAFLD) (35). In our case, we observed that an overweight girl with hyperinsulinemia developed type 2 DM in the 4th year.

The limitations of our study are that it was a retrospective and single centre study with some patients with a long-term follow-up. The WHO Health Organisation criteria adapted for children were used to define MetS. The WHO criteria adapted for children were used to define MetS, rather than the IDF 2007 criteria (36), because this consensus also suggests that MetS should not be diagnosed in children under 10 years of age and also because some of the patients in this retrospective study had missing waist circumference measurements.

In conclusion, both obese and overweight individuals are at risk for MetS and type 2 DM, and type 2 DM may develop during follow-up, even if not at admission. Considering that the foundations of many diseases encountered in adulthood are laid in childhood, attention should be paid to the warning signs of obesity and its complications and preventive measures should be taken.

Ethics Committee Approval: This study was approved by the Ethics Committee of Istanbul University, Faculty of Medicine (02.10.2013, File No:2013/1245).

Informed consent: The study was conducted retrospectively and was designed as an archived review of the files of all patients; it was neither necessary nor possible to acquire informed consent from the patients.

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REFERENCES

1. WHO Obesity and Overweight Fact Sheets (2017). p 3–7. Available online at http://www.who.int/mediacentre/factsheets/fs311/en/ (accessed 10 Aug, 2023)
2. National Child Measurement Programme. https://digital.nhs.uk/data-and-information/publications/statistical/national-child-measurement-programme/2020-21-school-year (Accessed 1 Sep 23)
3. Pinhas-Hamiel O, Hamiel U, Bendor CD, Bardugo A, Twig G, Cukierman-Yaffe T. The Global Spread of Severe Obesity in Toddlers, Children, and Adolescents: A Systematic Review and Meta-Analysis. Obes Facts. 2022;15(2):118-134. doi:10.1159/000521913
4. Görçin Karaketir Ş, Lüleci NE, Eryurt MA, Emecen AN, Haklıdır M, Hıdıroğlu S. Overweight and obesity in preschool children in Turkey: A multilevel analysis. J Biosoc Sci. 2023;55(2):344-366. doi:10.1017/S0021932022000025
5. Pekcan AG, Karaağaoğlu N, Samur FG. (2011). Türkiye de Okul Çağı Çocuklarında Büyümenin İzlenmesi Projesi TOÇBİ Raporu: TC Sağlık Bakanlığı yayınları.
6. T.C. Sağlık Bakanlığı. Türkiye çocukluk çağı (İlkokul 2. sınıf öğrencileri) şişmanlık araştırması COSI-TUR 2016. https://hsgm.saglik.gov.tr/depo/haberler/turkiye-cocukluk-cagi-sismanlik/COSI-TUR-2016-Kitap.pdf (Accessed Aug 22).

7. Türkiye Sağlıklı Beslenme ve Hareketli Hayat Programı" Sağlık Bakanlığı, Halk Sağlığı Genel Müdürlüğü, Ankara 2019 (Accessed Aug 22)
8. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med. 1998;15(7):539-553. doi:10.1002/(SICI)1096-9136(199807)15:7<539::AID-DIA668>3.0.CO;2-S
9. Cioana M, Deng J, Nadarajah A, Hou M, Qiu Y, Chen SSJ, et al. The Prevalence of Obesity Among Children With Type 2 Diabetes: A Systematic Review and Meta-analysis. JAMA Netw Open. 2022;5(12):e2247186. Published 2022 Dec 1. doi:10.1001/jamanetworkopen.2022.47186
10. Jolliffe CJ, Janssen I. Vascular risks and management of obesity in children and adolescents. Vasc Health Risk Manag. 2006;2(2):171-187. doi:10.2147/vhrm.2006.2.2.171
11. Magnussen CG, Koskinen J, Chen W, Thomson R, Schmidt MD, Srinivasan SR, et al. Paediatric metabolic syndrome predicts adulthood metabolic syndrome, subclinical atherosclerosis, and type 2 diabetes mellitus but is no better than body mass index alone: the Bogalusa Heart Study and the Cardiovascular Risk in Young Finns Study. Circulation. 2010;122(16):1604-1611. doi:10.1161/CIRCULATIONAHA.110.940809
12. Christian Flemming GM, Bussler S, Körner A, Kiess W. Definition and early diagnosis of metabolic syndrome in children. J Pediatr Endocrinol Metab. 2020;33(7):821-833. doi:10.1515/jpem-2019-0552
13. Urbina EM, Kimball TR, Khoury PR, Daniels SR, Dolan LM. Increased arterial stiffness was found in adolescents with obesity or obesity-related type 2 diabetes mellitus. J Hypertens. 2010;28(8):1692-1698. doi:10.1097/HJH.0b013e32833a6132
14. Type 2 diabetes in children and adolescents. American Diabetes Association. Diabetes Care. 2000 Mar;23(3):381-9. https://doi.org/10.2337/diacare.23.3.381.
15. Kurtoğlu S, Hatipoğlu N, Mazıcıoğlu M, Kendirici M, Keskin M, Kondolot M. Insulin resistance in obese children and adolescents: HOMA-IR cut-off levels in the prepubertal and pubertal periods. J Clin Res Pediatr Endocrinol. 2010;2(3):100-106. doi:10.4274/jcrpe.v2i3.100
16. Wang Q, Yin J, Xu L, Cheng H, Zhao X, Xiang H et al. Prevalence of metabolic syndrome in a cohort of Chinese schoolchildren: comparison of two definitions and assessment of adipokine as components by factor analysis. BMC Public Health. 2013;13:249. Published 2013 Mar 21. doi:10.1186/1471-2458-13-249
17. Shafiee G, Kelishadi R, Heshmat R, Qorbani M, Motlagh ME, Aminaee T et al. First report on the validity of a continuous Metabolic syndrome score as an indicator for Metabolic syndrome in a national sample of paediatric population-the CASPIAN-III study. Endokrynol Pol. 2013;64(4):278-284. doi:10.5603/ep.2013.0006
18. Cook S, Weitzman M, Auinger P, Nguyen M, Dietz WH. Prevalence of a metabolic syndrome phenotype in adolescents: findings from the third National Health and Nutrition Examination Survey, 1988-1994. Arch Pediatr Adolesc Med. 2003;157(8):821-827. doi:10.1001/archpedi.157.8.821
19. Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, Yeckel CW, et al. Obesity and metabolic syndrome in children and adolescents. N Engl J Med. 2004;350(23):2362-2374. doi:10.1056/NEJMoa031049
20. de Ferranti SD, Gauvreau K, Ludwig DS, Neufeld EJ, Newburger JW, Rifai N. Prevalence of the metabolic syndrome in American adolescents: findings from the Third National Health and Nutrition Examination Survey. Circulation. 2004;110(16):2494-2497. doi:10.1161/01.CIR.0000145117.40114.C7
21. Dündar İ, Akıncı A. Prevalence of type 2 diabetes mellitus, metabolic syndrome, and related morbidities in overweight and obese children. J Pediatr Endocrinol Metab. 2022;35(4):435-441. Published 2022 Jan 17. doi:10.1515/jpem-2021-0271
22. Sangun Ö, Dündar B, Köşker M, Pirgon Ö, Dündar N. Prevalence of metabolic syndrome in obese children and adolescents using three different criteria and evaluation of risk factors. J Clin Res Pediatr Endocrinol. 2011;3(2):70-76. doi:10.4274/jcrpe.v3i2.15
23. Atabek ME, Eklioğlu BS, Akyürek N. Reevaluation of the prevalence of metabolic syndrome in an urban area of Turkey. J Clin Res Pediatr Endocrinol. 2013;5(1):50-54. doi:10.4274/Jcrpe.778
24. Cizmecioglu FM, Etiler N, Hamzaoglu O, Hatun S. Prevalence of metabolic syndrome in schoolchildren and adolescents in Turkey: a population-based study. J Pediatr Endocrinol Metab. 2009;22(8):703-714. doi:10.1515/jpem.2009.22.8.703
25. Sen Y, Kandemir N, Alikasifoglu A, Gonc N, Ozon A. Prevalence and risk factors of metabolic syndrome in obese children and adolescents: the role of the severity of obesity. Eur J Pediatr. 2008;167(10):1183-1189. doi:10.1007/s00431-007-0658-x
26. Irakoze L, Manirakiza A, Zhang Y, Liu J, Li J, Nkengurutse L et al. Metabolic Syndrome in the Offspring of Parents with Metabolic Syndrome: A Meta-Analysis. Obes Facts. 2021;14(1):148-162. doi:10.1159/000513370
27. Liese AD, Mayer-Davis EJ, Tyroler HA, Davis CE, Keil U, Schmidt MI, et al. Familial components of the multiple metabolic syndrome: the ARIC study [published correction appears in Diabetologia 1998 May;41(5):608]. Diabetologia. 1997;40(8):963-970. doi:10.1007/s001250050775
28. Ten S, Maclaren N. Insulin resistance syndrome in children. J Clin Endocrinol Metab. 2004;89(6):2526-2539. doi:10.1210/jc.2004-0276
29. Nur Zati Iwani AK, Jalaludin MY, Roslan FA, Mansor F, Md Zain F, Hong JYH, et al. Cardiometabolic risk factors among children affected by overweight, obesity, and severe obesity. Front Public Health. 2023;11:1097675. Published 2023 Apr 27. doi:10.3389/fpubh.2023.1097675
30. Guran T, Turan S, Akcay T, Bereket A. Significance of acanthosis nigricans in childhood obesity. J Paediatr Child Health. 2008;44(6):338-341. doi:10.1111/j.1440-1754.2007.01272.x
31. Kjellberg E, Roswall J, Bergman S, Almqvist-Tangen G, Alm B, Dahlgren J. The longitudinal birth cohort study found that a significant proportion of children had abnormal metabolic profiles and insulin resistance at 6 years of age. Acta Paediatr. 2019;108(3):486-492. doi:10.1111/apa.14599
32. Morrison JA, Glueck CJ, Umar M, Daniels S, Dolan LM, Wang P. Hyperinsulinemia and metabolic syndrome at the mean age of 10 years in black and white schoolgirls and development of impaired fasting glucose and type 2 diabetes mellitus by the mean age of 24 years. Metabolism. 2011;60(1):24-31. doi:10.1016/j.metabol.2009.12.013
33. Cioana M, Deng J, Nadarajah A, Hou M, Qiu Y, Chen SSJ, et al. The Prevalence of Obesity Among Children With Type 2 Diabetes: A Systematic Review and Meta-analysis. JAMA Netw Open.

2022;5(12):e2247186. Published 2022 Dec 1. doi:10.1001/jamanetworkopen.2022.47186

34. Babaoğlu K, Hatun S, Arslanoğlu I, Işgüven P, Baş F, Ercan O et al. Evaluation of glucose intolerance in adolescents relative to adults with type 2 diabetes mellitus. J Pediatr Endocrinol Metab. 2006;19(11):1319-1326. doi:10.1515/jpem.2006.19.11.1319
35. Jaruratanasirikul S, Thammaratchuchai S, Puwanant M, Mo-Suwan L, Sriplung H. Progression from impaired glucose tolerance to type 2 diabetes in obese children and adolescents: a 3-6-year cohort study in southern Thailand. J Pediatr Endocrinol Metab. 2016;29(11):1267-1275. doi:10.1515/jpem-2016-0195
36. Zimmet P, Alberti KG, Kaufman F, Tajima N, Silink M, Arslanian S et al. IDF Consensus Group. The metabolic syndrome in children and adolescents: an IDF consensus report. Pediatr Diabetes. 2007 Oct;8(5):299-306. doi: 10.1111/j.1399-5448.2007.00271.x. PMID: 17850473.

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RESEARCH ARTICLE

Mothers' Attitudes Toward Sun Protection for Children Aged 3-6 Years

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ABSTRACT

Objective: Reducing ultraviolet radiation exposure is important for preventing skin cancer. Parents' behaviors can reduce the risk of their children developing skin cancer in the future. In this study we evaluated the knowledge and attitudes of mothers with children aged 3-6 years regarding sun protection behaviors.

Methods: The study was conducted at the Family Medicine outpatient clinics of Şişli Hamidiye Etfal Training and Research Hospital in Turkey. A data form with 20 questions was administered to the participants which assesses demographic data, attitudes toward sun protection, sources of sun-related information, and knowledge about sunscreen. A p-value<0.05 was considered significant.

Results: The study included 278 participants with a mean age of 33.05 years. Of them, 61.2% (n: 170) had at least a high school education, 30.2% (n: 84) were white-collar workers, and 12.6% (n: 35) were blue-collar workers. While 87.2% (n: 242) reported taking sun protection measures, 60.4% (n: 168) used sunscreen for their children. The most common method was wearing a hat (82.7%, n: 230). The mean knowledge score was 10.14 ± 3.92 (min: 0, max: 18), No one could give correct answers to the questions. The most frequently incorrect item was "sunscreen should only be used in summer." Most mothers' source of information were healthcare professionals (%71, n: 199). Mothers who had more than one child, had higher education, and were white-collar workers had higher scores (p< 0.05). Sunscreen users had higher knowledge scores than non-users (p< 0.05).

Conclusions: While most mothers reported taking sun protection measures, their knowledge was insufficient. Healthcare professionals, as a key source of information for mothers, should be more educating them during the routine follow-ups.

Keywords: Children, parents, sun-related behaviors, sun protection

INTRODUCTION

Skin cancer is one of the most commonly diagnosed cancers worldwide. In the United States, approximately 5 million individuals undergo skin cancer treatment annually (1). Despite the increasing incidence of skin cancer in recent years, it is considered one of the most preventable malignancies (2). Risk factors for skin cancer can be classified as modifiable and non-modifiable (1). Excessive exposure to ultraviolet radiation (UVR) from sunlight, indoor tanning devices, overexposure to the sun (including sunburn), weakened immune system, and genetic predisposition increase the risk of various types of skin cancer (1). UVR exposure is a modifiable factor, and lifestyle changes such wearing protective clothing (long-sleeved shirts, hats), using sunscreen, and avoiding the sun during 10 a.m.-4 p.m.-can minimize it (1-3).

Young children and elderly adults are particularly sensitive to sunlight (4). Children are especially sensitive because they depend entirely on their parents to protect them from the sun (5, 6). Most exposure to solar radiation occurs during childhood, and early-life exposure is a contributes to an increased risk of melanoma later in life (2, 7, 8). For these reasons, sun protection is important for children and adolescents (1, 2).

The formation of health-related behavior patterns begins in early childhood, and the behaviors exhibited by parents are critical during these years (2, 9). Parents should actively practice safe behaviors to protect their children from the sun and ensure they provide sunscreen, hats, and sunglasses for their children (5, 10). Parental attitudes also serve as a role model for children's attitudes and behaviors toward sun safety (5, 6). Educating parents and increasing their awareness about this issue can effectively protect children from the harmful effects of the sun.

Therefore, this study evaluated mothers' knowledge of sun protection behaviors and their attitudes toward sun protection.

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MATERIALS AND METHODS

This single-center, descriptive study was conducted at the Family Medicine outpatient clinics Şişli Hamidiye Etfal Training and Research Hospital in Turkey between April 1, 2021 and July 1, 2021.

Study population and sample

This study included mothers with children aged 3-6 years who visited the Family outpatient clinics of Şişli Hamidiye Etfal Training and Research Hospital for any reason between April 1, 2021 and July 1, 2021. The sample size was calculated with 95% reliability for over 1000 people who were likely to apply to the outpatient clinics between these dates. It was planned to reach a minimum of 278 people according to the sample size calculation.

Ethics committee approval

Ethical committee approval was obtained from the Şişli Hamidiye Etfal Training and Research Hospital Clinical Research Ethics Committee the Health Science University (dated 02/03/2021 and numbered 3179).

Data collection

Our team questioned participants who provided informed consent via face-to-face interviews**.** The first part of the data form provided the information of the participants, mothers' and their children's ages (the children who were with their mothers during the interviews and were considered in responses), mothers' educational status, whether they take sun protection measures for their children, their use of sunscreen, their opinions on sun protection methods, sources of knowledge about sun protection, and what they did when they noticed sunburn symptoms. The second part of the data form consisted of three-point Likert-type propositions created by the researchers, to evaluate mothers' knowledge about the effects of the sun on their skin, sunscreen, and protection from the harmful effects of the sun. Participants responded to these propositions with "Yes," "No," and "I Don't Know." Each correct answer given to these 20 propositions was scored as "1" point, while incorrect answers were scored as a "0" point; thus the mothers' knowledge levels were evaluated. When the responses to these propositions were evaluated by Cronbach's Alpha analysis, the alpha coefficient was found to be 0.746. In the literature, values of 0.7 and above are considered reliable for Cronbach's alpha's analysis (11).

The exclusion criteria were any psychiatric diagnoses, communication impediments, or refusal to participate in the research.

Statistical analysis

In the data obtained from the study, descriptive statistics are presented as; frequency distribution and percentage for categorical data and, as mean, standard deviation, minimum, and maximum for numerical data. The distribution of data was assessed using the Kolmogorov-Smirnov test. The Pearson chi-square test was used for comparisons of descriptive groups. Nonparametric tests were employed for data that did not exhibit normal distribution. Independent two-group comparisons of numerical variables were conducted using the Student t-test when the normality assumption was met and, the Mann-Whitney U test when the normality assumption was not met. Descriptive group comparisons were performed using Pearson's chi-squared test, Fisher's exact test, and the independent t-test. For correlation analysis, Pearson's correlation coefficient was used to evaluate the relationship between two continuous variables that were normally distributed. In cases in which the data did not follow a normal distribution, Spearman's rank correlation coefficient was applied to assess the strength and direction of the association between variables. Data analysis was performed using the SPSS 25.0 package, and p values of <0.05 were considered indicative of statistical significance.

RESULTS

A total of 278 mothers participated in the study, and their mean age was 33.05 ± 5.4 years (min: 21; max: 46). The number of children that mothers had was a minimum of 1 and a maximum of 8. The main age of the children was 4.18 ± 1.12 years (min: 3; max: 6). Of the mothers, 61.2% (n: 170) had a high school education or above, 37.4% (n: 104) had an education below high school, and 1.4% (n: 4) were illiterate. Most of the mothers were unemployed (57.2%, n: 159) while, 30.2% (n: 84) were white-collar workers, and 12.6% (n: 35) were blue-collar workers. In addition, 9 mothers (3.2%) had a family member with skin cancer.

Regarding sunscreen use, 54.7% of the mothers (n: 152) reported using sunscreen for themselves, with Sun Protection Factor (SPF) 50 being the most used factor (n: 101, 36.3%); and 168 mothers (60.4%) reported using sunscreen for their children, with SPF 50 being the most commonly used factor for children as well (n: 141, 50.7%). The use of sunscreen for children was higher among those who were employed, had a high school education or above, had higher income levels, and had more than one child (p: 0.000; 0.000; 0.000, 0.032, respectively). The rate of sunscreen use among children was higher among mothers who used sunscreen on their own. This difference was statistically significant (p: 0.000).

In addition, 87.2% of the mothers (n: 242) stated that they took preventive measures to protect their children from the sun, while 8.6% (n: 24) stated that the sun was harmless and that protection was unnecessary. The most common measures reported by mothers were wearing a hat (82.7%, n: 230), using sunscreen (60.1%, n: 167), and keeping their children in shaded areas when the sun is at its peak time (51.4%, n: 143). Figure 1 shows the mothers' responses to the question about their sources of information on sun protection.

When asked whether their child had a history of sunburn, 7.6% of the mothers (n: 21) reported that their child had previously experienced sunburn. In addition, 60.8% (n: 169) of the mothers stated that they would seek medical attention first when their child showed symptoms of sunburn, whereas 28.4% (n: 79) stated that they would use medications available at home, 15.5% (n: 43) used traditional remedies such as yogurt or toothpaste, and 9.4% (n: 26) said they would do nothing as they believed it would heal on its own.

Table 1 presents the distribution of mothers' responses to Likert-type statements regarding their knowledge. Their knowledge mean score 10.14 ± 3.92 (min: 0, max: 18). No mother achieved a perfect score. Among the statements assessing their knowledge, the highest number of correct responses from mothers was for the item "a special sunscreen for children should be used because their skin is more sensitive," while the highest number of incorrect responses was for the item "sunscreen should be used only in summer."

There was no statistically significant relationship between the mothers' knowledge scores and the ages of the mothers and their children (p > 0.05). However, there was a statistically significant negative correlation between their total knowledge scores and the number of children (p: 0.012, r: -0.151). Among the mothers, those who were white-collar workers had a significantly higher knowledge score than those who were blue-collar workers and those who were not employed (p: 0.005, p: 0.000, respectively). In addition, mothers with a high school education or higher education had significantly higher knowledge scores than those with less than a high school education (p: 0.000).

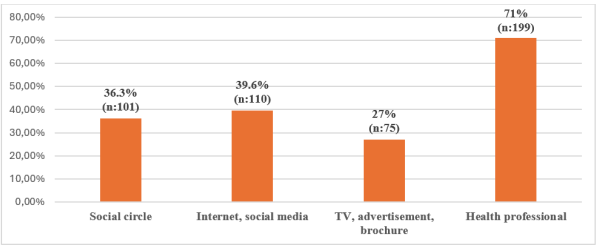

Figure 1: Sources of information on sun protection among mother.

No significant relationship was found in the mothers' knowledge scores based on whether their family had a history of skin cancer or whether their children had previously experienced sunburn (p > 0.05).

There was no statistically significant difference between the mothers' knowledge scores according to whether they took sun protection measures for their children (p > 0.05). However, among the mothers, those who used hats, sunscreen, and covered the baby stroller to protect their children from the sun had significantly higher knowledge scores than those who did not take these measures (p: 0.005, p: 0.000, p: 0.001, respectively). There was no significant relationship between the knowledge scores of mothers who used protection methods, such as wearing long clothing or staying indoors when the sun was at its peak time and those who did not use these methods (p > 0.005). In addition, mothers who used sunscreen for themselves and/or their children had significantly higher knowledge scores than those who did not use sunscreen (p: 0.000, p: 0.000, respectively).

Table 1. Participants' responses to the propositions

	Yes n (%)	No n (%)	I do not know. n (%)
The harmful rays of the sun can cause skin cancer, so sunscreen should be used.	196 (70.5%)	24 (8.6%)	58 (20.9%)
As the duration of sun exposure increases in children, the risk of skin cancer is higher than that in to adults.	165 (59.4%)	20 (7.2%)	93 (33.5%)
A special sunscreen for children should be used because their skin is sensitive.	223 (80.2%)	19 (6.8%)	36 (12.9%)
Sunlight weakens the immune system.	52 (18.7%)	139 (50%)	87 (31.3%)
Use of sunscreen does not reduce the beneficial effects of sunlight.	124 (44.6%)	68 (24.5%)	86 (30.9%)
Using sunscreen does not reduce the production of vitamin D, which is produced by direct contact with skin.	118 (42.5%)	64 (23%)	96 (36.5%)
The beneficial effects of sunlight cannot be obtained through window glass.	186 (64.9%)	49 (17.6%)	43 (15.5%)
The time required to benefit from the positive effects of sunlight is at least 20 min.	201 (72.3%)	25 (9%)	52 (18.7%)
Sunscreen should be used only during summer.	148 (53.2%)	90 (32.4%)	40 (14.4%)
Sunscreen should be applied before entering the sea.	100 (36%)	151 (54.3%)	27 (9.7%)
Sunscreen should be applied between 10:00 AM and 16:00 PM	156 (56.1%)	69 (24.8%)	53 (19.1%)
It is recommended to wait 15-30 minutes after applying sunscreen before going outside.	173 (62.2%)	36 (12.9%)	69 (24.8%)
Sunscreen should be reapplied after every contact with water.	160 (57.6%)	50 (18%)	68 (24.5%)
Sunscreen should be reapplied every 2-3 hours.	154 (55.4%)	50 (18%)	74 (26.6%)
Prolonged exposure to the sun with sunscreen is dangerous.	148 (53.2%)	48 (17.3%)	82 (29.5%)
Fair-skinned individuals are more sensitive to the sun and are prone to skin cancer.	191 (68.7%)	13 (4.7%)	74 (26.8%)
Dark-skinned people do not get sunburn.	91 (32.7%)	121 (43.5%)	66 (23.7%)
Tanned skin does not protect against sunlight.	123 (44.2%)	53 (19.1%)	102 (36.7%)
Tanning is evidence of skin damage.	101 (36.3%)	87 (31.3%)	90 (32.4%)
Avoiding sun exposure at regular intervals does not prevent sunburn.	118 (42.4%)	75 (27%)	85 (30.6%)

DISCUSSION

In this study, which evaluated the knowledge, attitudes, and behaviors of mothers regarding methods for protecting their children from the sun, most mothers reported using a method to protect their children from the sun; however, their level of knowledge on the subject was found to be insufficient.

Early childhood is the stage during which fundamental personality traits, behaviors, and habits are formed. It is widely acknowledged as the most active phase of a child's development, with behaviors established during this time often continuing into adulthood (2, 9). Parents' knowledge and approaches to sun protection methods are important because they can reduce the risk of their children developing skin cancer in the future and help them acquire correct behavioral patterns throughout their lives.

Multiple methods have been recommended for sun protection, including wearing protective clothing, hats, sunglasses, keeping in shade, and minimizing time spent outdoors (12). In a study examining sun protection methods used for children, hat use was found to be the most common method, followed by avoiding sun exposure between 10:00 AM and 4:00 PM and using sunscreen, respectively (13). Another study evaluating sun protection methods among children aged 6-18 found that approximately 85% of children used at least one sun protection method, with wearing long-sleeved clothing being the most common method for girls and wearing hats being most common method for boys. The least used method in both genders was sunscreen application (14). In our study, 87.2% of the mothers used at least one method to protect their children from the sun, and the most common methods were hat use, sunscreen application, and avoiding sun exposure during peak hours. These results are consistent with those reported in literature. The differences in the ranking of these sun protection methods may be attributed to variations in knowledge and sociodemographic factors.

In our study, the predominance of health personnel as the primary source of information for mothers underscores the significant role of health professionals in creating awareness about sun protection, as demonstrated in other studies (6, 15, 16). However, in a study of pediatricians, although over 90% of them believed that skin cancer is a public health issue and that protection from sun exposure during childhood reduces the risk of melanoma in adulthood, only 22.3% reported providing counseling on sun protection for all age groups (17). Considering the impact of healthcare professionals in this regard, they should be encouraged to provide parents with information on sun protection, and the process should be supported through public awareness campaigns.

The mean knowledge score of the mothers was 10.14 ± 3.92, and no mother achieved a perfect score. This result indicates a deficiency of parental knowledge on this topic. Similarly, a study conducted in Turkey found that mothers had relatively low levels of knowledge regarding the harmful effects of the sun and appropriate sun protection behaviors. It was observed that mothers' knowledge levels on this subject were not influenced by several factors, such as age, educational level, employment status, number of children, family type, and health insurance coverage (18). However, our study determined that mothers' knowledge levels were associated with their employment status, educational level, and income levels. Moreover, the decrease in their knowledge scores as the number of their children increased may stem from differences in the time and attention mothers allocate to their children relative, to those with only one child. The fact that half of the mothers believed that sunscreen should be used only in summer could be considered an indicator that not only a lack of knowledge exists, but that the content of knowledge needs to be expanded.

The World Health Organization recommends starting habits for protection from UVR in the early life of children and teaching these habits as part of routine preventive health services for effective sun protection, which is the simplest and most feasible way to prevent skin cancer (19). Among different countries, Australia has developed successful strategies to monitor and reduce the frequency of skin cancer after recognizing that childhood exposure to the sun is a significant risk factor for its development (20). In France, melanoma prevention programs have been implemented for a long time (21). The U.S. The Preventive Services Task Force (USPSTF) recommends that clinicians counsel young adults, adolescents, children, and parents of young children with fair skin types aged 6 months to 24 years to minimize UVR exposure and reduce the risk of skin cancer (18, 22).

In Turkey, there are no educational programs aimed at conveying accurate information or correcting misconceptions about sun protection among children. In a randomized controlled trial conducted under the program "Protecting My Child from the Sun," parents with children aged 3-6 years were divided into three groups: a control group, an educated group, and a group receiving education along with short message reminders. The group that received education along with short message reminders showed the greatest increase in sun protection behaviors for their children, indicating the positive impact of informing parents through such programs (23). In our study, mothers who used sunscreen themselves were more likely to use sunscreen for their children**.** Parental implementation variations directly affect the safety of their offspring. However, when providing recommendations to individuals, their socioeconomic status should be considered and supported using appropriate methods.

A strength of this study is the identification of the target population. By focusing on the mothers of children aged 3-6, the research highlights the importance of parental attitudes in shaping health-related behaviors in this age group. Additionally, by providing valuable insights into sun protection behaviors, this study demonstrates that this study can yield practical results for public health education and cancer prevention strategies. The prominence of healthcare workers as the primary source of information for mothers offers important clues to areas in which future educational efforts should be concentrated.

The study also has some limitations. First, the study was conducted in a single hospital setting; thus, it may be difficult to generalize the findings to other regions or different socioeconomic and cultural settings. Second, interviews with mothers alone did not assess the role of fathers or other caregivers in sun protection. This condition limits the full understanding of sun protection behaviors within family dynamics.

CONCLUSION

In conclusion, this study showed that most mothers took preventive measures to protect their children from the harmful effects of the sun; however, their overall level knowledge level was found to be insufficient. The fact that healthcare professionals are the primary source of information for mothers highlights the importance of education and awareness efforts in this field. It is particularly important for healthcare professionals to provide more information to families about sun protection during routine follow-ups. Socioeconomic factors, such as mothers' level education level, employment status, and income level, were observed to influence their knowledge and behaviors regarding sun protection. Therefore, raising awareness of sun protection through targeted educational programs aimed at different segments of the population is of great importance. Furthermore, involving not only mothers but also fathers and caregivers in the process could contribute to more comprehensive and effective outcomes.

Ethics Committee Approval: This study was approved by the Şişli Hamidiye Etfal Training and Research Hospital Clinical Research Ethics Committee the Health Science University (dated 02/03/2021 and numbered 3179).

Informed Consent: Written consent was obtained from the participants.

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REFERENCES

1. World Cancer Research Fund. Cancer Facts and Figures 2021. World Cancer Research Fund International. 2021. p. 1–4. Available at: https://www.wcrf.org/cancer-trends/worldwide-cancer-data/.
2. Thoonen K, van Osch L, Drittij R, de Vries H, Schneider F. A Qualitative Exploration of Parental Perceptions Regarding Children's Sun Exposure, Sun Protection, and Sunburn. Front Public Health. 2021;9:596253. doi:10.3389/fpubh.2021.596253.
3. Suozzi K, Turban J, Girardi M. Focus: Skin: Cutaneous Photoprotection: A Review of the Current Status and Evolving Strategies. Yale J Biol Med. 2020;93(1):55.
4. Merin KA, Shaji M, Kameswaran R. A Review on Sun Exposure and Skin Diseases. Indian J Dermatol. 2022;67(5):625. doi: 10.4103/ijd.ijd_1092_20.
5. Dadlani C OS. Planning for a brighter future: a review of sun protection and barriers to behavioral change in children and adolescents. Dermatol Online J. 2008;14(9):1.
6. Stanton WR, Janda M, Baade PD, Anderson P. Primary prevention of skin cancer: a review of sun protection in Australia and internationally. Health Promot Int. 2004;19(3):369-378. doi:10.1093/heapro/dah310.
7. Tekbaş ÖF, Şimşek İ, Kaymak Y. Üniversite öğrencilerinin güneşten korunma ile ilgili bilgi tutum ve davranışları. Türkderm-Deri Hast ve Frengi Arşivi.2007;41(3):81–5.
8. Gandini S, Autier P, Boniol M. Reviews on sun exposure and artificial light and melanoma. Prog Biophys Mol Biol. 2011;107(3):362-366. doi:10.1016/j.pbiomolbio.2011.09.011.
9. Arslan A. Family in Supporting the Development of the Child in Early Childhood. Gümüşhane Univ J Health Sci. 2022;11(4):1676-1684.
10. American Academy of Dermatology Association. Sunscreen Faqs. [cited 2023 Jun 14]. Available at: https://www.aad.org/public/everyday-care/sun-protection/shade-clothing-sunscreen/sunscreen-faqs.
11. Kılıç S. Cronbach'ın alfa güvenirlik katsayısı. Journal of Mood Disorders. 2016;6(1):47–48.
12. Henderson SI, King KL, Karipidis KK, Tinker RA, Green AC. Effectiveness, compliance and application of sunscreen for solar ultraviolet radiation protection in Australia. Public Health Res Pract. 2022;32(1). doi:10.17061/phrp3212205.
13. Baz K, Köktürk A, İkizoğlu G, Buğdaycı R, Kaya Tİ, Koca A. Sun Protection Knowledge and Attitudes of Adults About Their Children. Turkiye Klin J Dermatol. 2003;13(2):101-107.
14. Nouri N, Iravani P, Abtahi-Naeini B. Sun protection behaviors among children aged 6-18 years old, the role of socioeconomic factors: A cross-sectional study. Health Sci Rep. 2023;6(11). doi:10.1002/hsr2.1727.
15. Balk SJ. Sun Protection. Pediatr Rev. 2023;44(4):236-239. doi:10.1542/pir.2022-005545.
16. Reinau D, Meier C, Gerber N, Hofbauer GF, Surber C. Sun protective behaviour of primary and secondary school students in North-Western Switzerland. Swiss Med Wkly. 2012;142. doi:10.4414/smw.2012.13520
17. Balk SJ, O'Connor KG, Saraiya M. Counseling parents and children on sun protection: a national survey of pediatricians. Pediatrics. 2004;114(4):1056-1064. doi:10.1542/peds.2004-1305.
18. Ergin A, Bozkurt Aİ, Bostancı M, Önal Ö. Assessment of knowledge and behaviors of mothers with small children on the effects of the sun on health. Pamukkale Med J. 2011;4(2):72-78.
19. Stockfleth E, Revol O. Encouraging sun protection early in life: from a successful prevention programme in children to the identification of psychological barriers in adolescents. J Eur Acad Dermatology Venereol. 2022;36(S6):12–21. doi: 10.1111/jdv.18194.
20. Edlich RF, Winters KL, Cox MJ, Becker DG, Horowitz JH, Nichter LS, et al. National Health Strategies to Reduce Sun Exposure in

Australia and the United States. J Long Term Eff Med Implants. 2004;14(3):215–24. doi: 10.1615/jlongtermeffmedimplants.v14.i3.60.

21. Del Marmol V, Ortonne JP. Groundwork for the prevention of melanoma in Europe. J Eur Acad Dermatology Venereol. 2015;29(s2):1. doi: 10.1111/jdv.12947.
22. US Preventive Services Task Force; Grossman DC, Curry SJ, Owens DK, Barry MJ, Caughey AB, Davidson KW, et al. Behavioral counseling to prevent skin cancer: US preventive services task force recommendation statement. JAMA. 2018;319(11):1134–1142. doi: 10.1001/jama.2018.1623.
23. Sümen A, Öncel S. The effect of 'I am Protecting my Child from the Sun'programme on parental sun protection behaviours: Randomized controlled trial. Journal of Advanced Nursing, 2021;77(1):387-400. doi: 10.1111/jan.14614.

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RESEARCH ARTICLE

Clinical Characteristics of Patients Initiated on Long-Term Noninvasive Ventilation Support: A Single-Center Experience

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ABSTRACT

Objective: Long-term noninvasive ventilation (NIV) support is increasingly being used by pediatricians for children with complex medical diseases. However, data on NIV support among children in Turkiye are limited.

Methods: This study included children who received long-term NIV support between July 2022 and July 2024 at a single center. Demographic and clinical characteristics and short-term clinical outcomes were retrospectively evaluated.

Results: A total of 30 patients were included. The median age at NIV initiation was 39.5 months (range: 9–108 months), and the most common underlying etiology was cardiovascular diseases (n = 9, 30%). Twenty-six patients were discharged with long-term NIV support, with a median discharge time of 5.5 days (range: 3–13 days) after NIV initiation. Of the 26 patients discharged with NIV support, four died during follow-up. Three patients, all of whom were from the cardiovascular group, no longer required respiratory support.

Conclusions: NIV can be used effectively for a wide variety of diseases in children. Understanding the current status of NIV support in our clinical setting may help us design a protocol to improve future outcomes.

Keywords: Noninvasive ventilation, pediatrics, cardiovascular diseases

INTRODUCTION

Noninvasive ventilation (NIV) delivers respiratory support via an interface that is applied noninvasively instead of an intubation tube or tracheostomy cannula(1). Noninvasive ventilation support is increasingly recognized by clinicians and used more frequently in pediatric practice because the number of children with special needs and/or chronic respiratory failure is increasing with advanced medical support (1). Noninvasive ventilation (NIV) can limit or delay the need for intubation for acute respiratory failure. Studies have also suggested that NIV aids in weaning from invasive ventilation, reduces intensive care unit (ICU) stay, decreases tracheostomy rates, decreases healthcare costs, and improves the quality of life for patients and caregivers(2-4).

Optimal ventilation requires a good balance between central respiratory drive, respiratory muscle work, and respiratory load. Any condition that disrupts one of these mechanisms, including upper and lower airway obstructions, chronic lung diseases, respiratory muscle diseases, and disorders affecting the control of central respiratory drive, are potential indications for NIV(1, 2, 4). The main methods for NIV support are continuous positive airway pressure (CPAP) and biphasic airway pressure (BPAP). While CPAP simply ensures continuous positive pressure and is used for patients with isolated upper/lower airway obstruction, BPAP delivers an additional positive pressure during inspiration. CPAP increases functional residual capacity and improves oxygenation and gas exchange; however, it does not support spontaneous inspiration. BPAP increases tidal volume and functional residual capacity (FRC), thereby

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improving gas exchange and ventilation more effectively. Biphasic airway pressure is the primary option for patients with central respiratory drive dysfunction and chronic hypercarbic respiratory failure (1, 2, 4). These patients have an increased respiratory load that causes hypoxia and hypoventilation leading to cor pulmonale, growth failure, and neurocognitive sequelae if not treated timely and efficiently(1).

The use of NIV outside intensive care units has dramatically improved over the last two decades. Noninvasive ventilation increases survival and slow respiratory functional decline without decreasing quality of life in patients with chronic respiratory failure. Although only a few randomized controlled studies have been conducted in this area, clinical practice has led to general acceptance of treating acute and chronic respiratory failure with NIV(5-8). Because NIV is rarely initiated outside intensive care units for chronic diseases in our country, our primary aim was to assess the clinical characteristics and short-term clinical outcomes of patients who were initiated on NIV during hospitalization and discharged home with long-term NIV support. Our secondary aim was to assess the factors affecting the success of NIV and to evaluate the short-term clinical outcomes of patients.

MATERIALS AND METHODS

The study included 30 patients who were started on long-term NIV support between July 2022 and July 2024. Long-term NIV was defined as needing NIV support for at least 6 hours per day for at least 3 weeks outside of an acute care setting(9). Patients who were already using NIV before hospital admission were not included in the study. We excluded critically ill patients with acute respiratory failure were not included. In addition, patients were excluded from the study if the families refused the initiation of noninvasive ventilation, did not cooperate, or if the patient was not compliant with the noninvasive ventilation.

Because pediatric polysomnography is not available in our center, the decision to initiate noninvasive ventilation is heavily based on blood gas analysis and clinical findings. Without polysomnography, chronic alveolar hypoventilation, which is often indicated by elevated $PaCO_2$ levels and clinical findings, plays a critical role in guiding treatment. The clinical signs of alveolar hypoventilation include recurrent respiratory infections, cor pulmonale, insomnia, frequent arousals, headaches, shortness of breath, fatigue, decreased intellectual performance, and growth failure(9-11).

During the first initiation of NIV, the patient is monitored and a control blood gas is administered 1 hour after initiation of NIV. If nighttime NIV is not sufficient to provide normocapnia, daytime NIV may be provided. The inspiratory positive airway pressure (IPAP) was increased according to the venous blood gas CO_2 levels. The expiratory positive airway pressure (EPAP) was set at a minimum of 4 cmH_2O and increased if needed according to the oxygen saturation of the patients. The inspiratory time and respiratory rate per minute were age-appropriate(12). All patients were closely followed up with pulse oximetry during the initiation of NIV. The awake morning control blood gas was obtained after the initiation of NIV.

Demographic and clinical characteristics of the patients, day of starting NIV at hospitalization, ventilator settings, mask type, day of discharge after NIV initiation, and short-term clinical outcomes were recorded. Ethical approval was obtained from the Ethics Committee of Basaksehir Cam and Sakura City Hospital (approval number E-96317027-514.10-224467097. Informed consent was obtained from the parents.

Statistical Analysis

The statistical analysis was performed using SPSS for Windows version 20.0. Normality was assessed using normality plots and the Kolmogorov-Smirnov test. Continuous variables that were normally distributed were presented as means and standard deviations, whereas data with asymmetrical distribution are presented as medians and 25-75 th percentiles. Categorical variables are presented as proportions. The statistical significance level was set at a p-value of <0.05.

RESULTS

The study included 30 patients with chronic respiratory distress who received long-term noninvasive ventilation support between July 2022 and July 2024. In 28 of the patients, NIV support was initiated as an inpatient, whereas 2 patients were initiated NIV at the outpatient clinic because the NIV equipment could not be obtained during hospitalization. The median age of patients at the time of NIV initiation was 39.5 (9-108) months; the youngest patient was 2 months old. Eleven patients (36.7%) were aged 1 year. Table 1 presents the baseline demographic and clinical characteristics of the patients.

The most common underlying etiology for NIV support was cardiovascular disease. The median age of the patients at the time of NIV initiation was 9 months (4-10 months) for cardiovascular diseases and 96 months (31-117 months) for neurological diseases. Table 2 presents the main underlying etiology of the NIV requirement.

Table 3 presents the descriptive features of NIV support. Approximately half of the patients (n=16) required NIV with oxygen support. The most common reason for initiating

Table 1. Clinical and demographic characteristics of the patients (n=30)

Age (months)	
Median (25-75 th percentile)	53 (17-120)
Age at NIV initiation (months)	
Median (25-75 th percentile)	39.5 (9-108)
Sex, n(%)	
Female	11 (36.7)
Male	19 (63.3)
Baseline respiratory support, n(%)	
None	27 (90)
Oxygen support	3 (10)
Baseline venous CO_2 levels (mmHg)	
Median, (25-75 th p)	53 (43-60)

NIV: Noninvasive ventilation support, CO_2: carbondioxide

Table 2. The underlying etiology of the NIV requirement (n=30)

The main underlying etiology of NIV requirements	n (%)	Age at initiation of NIV, months (median, 25-75 th p)
Cardiovascular diseases	9 (30)	9 (4-10)
Postoperative diaphragmatic paralysis	3	
Pulmonary hypertension	2	
Tracheobronchial compression	2	
Postoperative prolonged ventilatory support	2	
Neurological	8 (26.7)	96 (31-117)
Epilepsy	7	
Spina bifida	1	
Chronic lung disease	8 (26.7)	79.50 (17-110.50)
Bronchiolitis obliterans	5	
Cyhlothorax	1	
Bronchopulmonary dysplasia	1	
Primary ciliary dyskinesia	1	
Neuromuscular	2 (6.7)	64.50 (19-110)
Spinal muscular atrophy-1	1	
Myopathy	1	
Chest deformity	2 (6.7)	71 (34-108)
Rhizomelyic chondrodysplasia	1	
I-cell disease	1	
Anatomic upper airway obstruction (microretrognathia)	1 (3.3)	6

NIV: Noninvasive ventilation support

Table 3. Descriptive features of NIV support (n=30)

Respiratory support, n(%)	
NIV only	14 (46.7)
NIV and oxygen supplementation	16 (53.3)
Major reason for NIV initiation, n(%)	
Persistent respiratory distress	17 (56.7)
CO_2 retention	9 (30)
Atelectasis	3 (10)
Witnessed apnea	1 (3.3)
Day of hospitalization at the first initiation of NIV	
Median (25-75 th p)	28 (13.50-48)
Mode of NIV, n(%)	
BPAP ST	28 (93.3)
BPAP S	1 (3.3)
CPAP	1 (3.3)
The type of interface mask, n(%)	
Nasal	22 (73.3)
Oronasal	8 (26.7)
EPAP, cmH_2O	
Median (25-75 th percentile)	5 (4-6.5)
IPAP, cmH_2O	
Median (25-75 th percentile)	9 (8-12)
Back-up rate/minute	25 (20-25)

BPAP: Biphasic airway pressure, CPAP: continuous positive airway pressure, S: Spontaneous, ST: Spontaneous/timed, NIV: noninvasive ventilation, EPAP: expiratory positive airway pressure, IPAP: inspiratory positive airway pressure

NIV support was persistent respiratory distress during hospitalization (56.7%, n=17). The median number of days of NIV initiation was 28th day of hospitalization (13.50-48 days). The most commonly selected mode for NIV support was the BPAP ST mode, and the most commonly selected interface was the nasal mask (73.3%).

Table 4. Short-term clinical outcomes of the patients (n=30)

NIV requirement time at discharge (hours)	
Mean±SD	11.6 ±3.2
Current NIV requirement time (hours)	
Median (25-75 th percentile)	5.50 (0-8)
Venous CO_2 levels after NIV initiation (mmHg)	
Median (25-75 th percentile)	45 (40-50)
Median follow-up period after NIV initiation	
Median (25-75 th percentile)	204 (105-274)
Current status of the patients (n=26)	
Reduced need for NIV support	9 (30)
Increased need for NIV support	1 (3.3)
No need for respiratory support	3 (10)
Same as discharge	2 (6.7)
Can not tolerate NIV***	5 (16.7)
Lost to follow-up	2 (6.7)
Exitus	4 (13.3)

NIV: Noninvasive ventilation support, CO_2: carbondioxide
* Reduction in the required pressure or duration of BPAP
**Increased pressure requirement and prolonged BPAP support duration
***Can not tolerate NIV due to adherence problems

The median number of days of discharge after NIV initiation was 5.5 days (3-13 days). Twenty-six patients could be discharged with long-term NIV treatment. Four patients required invasive ventilation during follow-up and could not be discharged with NIV. One patient with rhizomelic chondrodysplasia was transferred to the ICU during follow-up, and two patients with congenital heart disease required invasive ventilation during hospitalization. Another patient with bronchiolitis obliterans initially tolerated NIV, but remained clinically unstable and ultimately required invasive ventilation, and died after ICU transfer. We did not observe any major side effects in any of the

26 patients. Of the 26 patients who were discharged with NIV support, four died during follow-up. Three of the 26 patients no longer needed any respiratory support, and all of these patients were in the cardiovascular (post-cardiac surgery) group. In nine of the 26 patients, the need for NIV support (pressures and/or time for NIV) had decreased. Twelve patients were still on NIV during the follow-up period. The final median EPAP value was 4.5 (4-5.75) cmH_2O while the median IPAP value was 9 (8-11) cmH_2O. There was no significant difference between the final and initial NIMV parameters($p>0.05$ for both). Table 4 presents the short-term clinical outcomes of the patients.

DISCUSSION

This study analyzed the demographic and clinical characteristics and short-term clinical outcomes of patients who were initiated on long-term NIV support at a single center. Although the use of NIV support in pediatric patients is increasing worldwide, it can still be initiated in only few centers in our country, especially outside the intensive care units. Increasing our knowledge in this area will result in a better understanding of NIV, as there is no standard protocol regarding long-term NIV initiation and follow-up programs for pediatric patients in our country.

NIV provides long-term ventilation support for children with a broad range of complex medical conditions, and NIV is a more acceptable alternative to invasive mechanical ventilation with tracheostomy for most of the families(13). The most common underlying etiology for the requirement of NIV was cardiovascular diseases, with a prevalence of 30 %, whereas chronic lung diseases (26.7%) and neurological diseases (26.7%) followed in our study. A systematic review including 289 studies reported that NIV was used for 73 medical conditions, with obstructive sleep apnea (OSA) (33%) and neuromuscular diseases (22%) being the most common causes(13). There are some possible explanations for the difference in the underlying diseases in our study based on the literature. First, our center has one of the largest cardiovascular and cardiac disease centers in Turkey, to which many patients are referred. In addition, we do not have a pediatric sleep center; therefore, we cannot perform polysomnography to diagnose OSA.

The median age at the time of NIV initiation was 39.5 (9-108) months, and 36.7% of the patients were aged 12 months. The age at the time of NIV initiation varies widely between previous studies. Castro-Cadesal et al.. reported the mean age at initiation of NIV as 8±3 years(13). Ikeda et al.. reported that patient age at NIV administration had a bimodal distribution, with a peak under 6 years old and a peak between 9 and 19 years in their study. They reported that neuromuscular disorders, such as severe respiratory distress associated with SMA type 1 or congenital abnormalities, may cause a peak incidence at age 6 years, whereas neuromuscular diseases like DMD, which complicate chronic respiratory failure during adolescence, cause a second peak between 9 and 19 years of age (14). Chatwin et al. reported a median age at initiation of NIV of 10 (3-15) years, and 56 % of the patients had neuromuscular disease in their retrospective cohort study including 496 children. In their study, thirteen percent (n=59) were younger than 1 year old(12). In our study, the median age at NIV initiation was younger than in previous studies. The most common etiology and youngest age group were cardiovascular diseases in our study, with a median age at NIV initiation of 9 months, which may explain the younger median age at NIV initiation in our study. Neurological diseases, predominantly epilepsy, constituted the oldest age group for NIV initiation in our study. Respiratory failure mostly occurs due to damage to the pulmonary parenchyma from aspiration or repetitive infections in this group, which may result in a greater need for ventilation support as the patients age. In addition, previous studies have reported that the median age of patients requiring invasive ventilation is younger than that of patients receiving NIV, as NIV is technically more difficult to adapt for small children(15). As our study is new, we may also suggest that NIV success may be increased by improving technical strategies, including interfaces, which have made a larger proportion of small children suitable for NIV over the years .

Nasal masks were the most commonly preferred interface type in our study (73.3%. Similar to our study, most previous studies have reported that nasal-type interfaces are often selected over oronasal and full-face interfaces(5, 13, 14). Nasal interfaces provide more comfortable respiratory support, a wider range of vision, a lower risk of vomiting aspiration, and greater ability to speak than oronasal and full-face interfaces. We did not use full-face interfaces in our study, as they are more difficult to perform in patients who were not sedated, as most of our patients' NIV support was initiated outside the intensive care unit. More than half of the patients (53.3%) required supplemental oxygen therapy in addition to NIV therapy. Amin et al. reported that 21.7 % of the patients required supplemental oxygen in addition to NIV support in their study, including 313 patients who required NIV during a 20-year period in Canada. They also reported that the most common indication for NIV support was neuromuscular disease(16). Ikeda et al. reported that 60 % of the patients with overall NIV required supplemental oxygen, whereas this rate was 37.7 % for neuromuscular patients on NIV, and there was a significant difference in oxygen requirement between neuromuscular and non-neuromuscular diseases(14). In our study, there were only 2 patients with neuromuscular diseases, and cardiac, neurological, and chronic lung diseases were the most common causes of NIV support with severe respiratory failure. NIV support may be initiated before hypoxia presents due to other clinical findings regarding alveolar hypoventilation in neuromuscular diseases. The most common mode of NIV was BPAP in our study. Similar to previous studies, CPAP is mostly preferred for upper airway obstruction, obesity, and obstructive sleep apnea, whereas BPAP therapy is preferred for patients with neuromuscular and neurological diseases, complex multiple medical conditions, and chronic lung diseases in our study(13). BPAP with a backup rate (ST mode) is the most commonly recommended method for neuromuscular, neurological, and chronic lung diseases (4).

In our study, 26 of 30 patients were discharged home with NIV, and the median discharge day after NIV initiation was 5.5 days.

The median day of hospitalization at the time of starting NIV was 28 days. After initiation of NIV, patients could be discharged with a median time of 5.5 days, which is a relatively short period for children with complex diseases. These results demonstrate the efficacy of NIV for the discharge of children with chronic, complex medical conditions. Four patients could not adapt to NIV, and three of these four patients were aged less than 12 months. It is much more difficult to find an appropriate interface for children and infants. Although there is no standard clinical validation study for limitation, a minimum weight of 5 kg is recommended for NIV treatment from some authors(4). Regarding the current status of the patients who could be discharged on long-term NIV, four of them died (13.3%), 10% did not need further ventilation support, and 16.7% had treatment failure during follow-up due to adherence problems in our study. A retrospective study including a 20-year period in Canada reported a mortality rate of 11% among patients on long-term NIV, whereas 9% of the patients no longer needed ventilation and 3% of the patients had treatment failure (16). In our study, treatment failure was relatively common during the short-term follow-up. As the median age of our patients was younger than that of previous studies, treatment failure during follow-up was not surprising. Another finding of our study was that all three patients who did not need longer respiratory support during follow-up were patients who required NIV after cardiovascular surgery. One patient had postoperative diaphragma paralysis, and two of them had tracheobronchial compression due to cardiovascular abnormalities. Similar to previous case reports, NIV is a successful option to avoid intubation after complications of cardiac surgery including diaphragma paralysis(17, 18). Even though the number of patients in our study was small, these results suggest that NIV may be very beneficial after cardiovascular surgery to bypass the acute period. A retrospective study including 200 patients with NIV reported that the NIV success rate was 85%, with a median duration of NIV of 3 days and mortality rate of 3.9 %(19). Our mortality rate is slightly higher than that of previous studies; however, as patients are younger and cardiac diseases are predominant in our study, mortality may be higher due to complications of the underlying diseases.

This study has some limitations. First, as our study is a single-center study, the sample size is relatively small. Second, polysomnography could not be performed for the titration of NIV support. Lastly, we could not demonstrate the long-term effects of NIV, including hospitalizations and side effects, because the study included a 2-year period.

CONCLUSION

Our study demonstrated the effects of NIV in children with complex medical conditions. Long-term NIV support is increasingly being used worldwide. Patients with cardiovascular diseases, especially during the post-surgery period, may benefit greatly from NIV support by avoiding intubation and intubation-related morbidities. As our patients' median age is younger than that in previous studies, we suggest that NIV support will soon become an increasingly acceptable choice for small children with the improvement of technologies. Although NIV is not appropriate for all children, it is an invaluable tool for the home care of children with chronic respiratory distress. There is a need for further studies to develop a national long-term NIV initiation program and standards of care for children on NIV.

Ethics Committee Approval: This study was approved by the ethics committee of the Ethics Committee of Basaksehir Cam and Sakura City Hospital (approval number E-96317027-514.10-224467097.

Informed Consent: Written consent was obtained from the participants.

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REFERENCES

1. Atag E, Krivec U, Ersu R. Noninvasive ventilation for children with chronic lung disease. Front Pediatr. 2020;11(8):561639.
2. Pavone M, Verrillo E, Caldarelli V, Ullmann N, Cutrera R. Noninvasive positive pressure ventilation in children. Early Hum Dev. 2013;89(Suppl 3):S25-31.
3. MacLean JE, Fauroux B. Long-term noninvasive ventilation in children: Transition from hospital to home. Paediatr Respir Rev. 2023;(47):3-10.
4. Amaddeo A, Frapin A, Fauroux B. Long-term noninvasive ventilation in children. Lancet Respir Med. 2016;(12):999-1008.
5. Chatwin M, Bush A, Simonds AK. Outcomes of goal-directed noninvasive ventilation and mechanical insufflation/exsufflation in spinal muscular atrophy type I. Arch Dis Child. 2011;96(5):426-32.
6. Ishikawa Y, Miura T, Ishikawa Y, Aoyagi T, Ogata H, Hamada S et al. Duchenne muscular dystrophy: survival by cardio-respiratory interventions. Neuromuscul Disord. 2011;21(1):47-51.
7. Oskoui M, Levy G, Garland CJ, Gray JM, O'Hagen J, De Vivo DC,et al. The natural history of spinal muscular atrophy type 1. Neurology. 2007;69(20):1931-6
8. McDougall CM, Adderley RJ, Wensley DF, Seear MD. Long-term ventilation in children: longitudinal trends and outcomes. Arch Dis Child. 2013;98(9):660-5.
9. Praud JP. Long-Term Non-invasive Ventilation in Children: Current Use, Indications, and Contraindications. Front Pediatr. 2020;5(8):584334.
10. Mayer OH, Amin R, Sawnani H, Shell R, Katz SL; RIND Study Group. Respiratory Insufficiency in Neuromuscular Disease (RIND): A Delphi Study to Establish Consensus Criteria for Define and Diagnose Hypoventilation in Pediatric Neuromuscular Disease. J Neuromuscul Dis. 2023;10(6):1075-1082.

11. Berry RB, Quan SF, Abreu AR, Bibbs ML, DelRosso L et al. The AASM Manual for Sleep Scoring and Associated Events: Rules, Terminology and Technical Specifications. American Academy of Sleep Medicine; 2020
12. Chatwin M, Tan HL, Bush A, Rosenthal M, Simonds AK. Long-term noninvasive ventilation in children: impact on survival and transition to adult care. PLoS One. 2015;10(5):e0125839.
13. Castro-Codesal ML, Dehaan K, Featherstone R, Bedi PK, Martinez Carrasco C, Katz SL, et al. . Long-term noninvasive ventilation therapies for children: A scoping review. Sleep Med Rev. 2018;37:148-158.
14. Ikeda A, Tsuji M, Goto T, Iai M. Long-term home noninvasive positive pressure ventilation in children: Results from a single center in Japan. Brain Dev. 2018;40(7):558-565.
15. Racca F, Berta G, Sequi M, Bignamini E, Capello E, Cutrera R, et al.; LTV Pediatric Italian Network. Long-term home ventilation of children in Italy: a national survey. Pediatr Pulmonol. 2011;46(6):566-72.
16. Amin R, Sayal P, Syed F, Chaves A, Moraes TJ, MacLusky I. Pediatric long-term home mechanical ventilation: 20 years of follow-up at one Canadian center. Pediatr Pulmonol. 2014;49(8):816-24.
17. Oktem S, Cakir E, Uyan ZS, Karadag B, Hamutcu RE, Kiyan G et al. Diaphragmatic paralysis after pediatric heart surgery: usefulness of non-invasive ventilation. Int J Pediatr Otorhinolaryngol. 2010;74(4):430-1.
18. Kovacikova L, Dobos D, Zahorec M. Noninvasive positive pressure ventilation for bilateral diaphragm paralysis after pediatric cardiac surgery. Interact Cardiovasc Thorac Surg. 2009;8(1):171-2.
19. Fernández Lafever S, Toledo B, Leiva M, Padrón M, Balseiro M, Carrillo A, López-Herce J. Non-invasive mechanical ventilation after heart surgery in children. BMC Pulm Med. 2016;16(1):167.

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RESEARCH ARTICLE

Evaluation of Risk Factors, Etiology, Diagnosis, and Auxiliary Diagnostic Methods of Children With Recurrent Wheezing Between 1-24 Months

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ABSTRACT

Objective: Wheezing should be evaluated separately from recurrent lower respiratory tract infections in terms of both etiology and risk factors. Early initiation of etiologic studies and good identification of risk factors are important in terms of the prognosis of the disease.

Methods: In this study, children between the ages of 1-24 months who had at least three recurrent wheezing attacks or who had wheezing lasting more than 1 month were examined. Cases who received a specific diagnosis for recurrent wheezing or were followed up as one of the wheezing phenotypes were compared. Between 2010 and 2012, the files of children between 1 and 24 months who had at least three recurrent wheezing attacks or who had wheezing lasting more than 1 month were examined at the Istanbul Medeniyet University Göztepe Training and Research Hospital. A total of 970 files were scanned and 76 cases were included in the study. The cases were examined by file scan and families were called by phone for incomplete information. History, socioeconomic/demographic characteristics, physical examination findings, laboratory and imaging results, and etiological causes were retrospectively recorded.

Results: In 76 cases with repeated wheezing in this study; early transient wheezing was 16% (n=12), persistent atopic wheezing was 21% (n=16), non-atopic wheezing was 25 % (n=19), and specific diagnosed cases were 38% (n=29). When all cases were taken into consideration, an echocardiogram was performed in 79% of cases, thoracic CT in 26% of cases, videofluoroscopy in 5%, and esophagus-stomach-duodenum X-ray in 25% of cases, pHmeter in 34% and bronchoscopy in 8% of cases. In the group of 29 people who received a specific diagnosis with these diagnostic and imaging techniques; gastroesophageal reflux disease (GERD) 44% (n=13), aspiration pneumonia secondary to GERD 7% (n=2), GERD + oropharyngeal dysfunction 10% (n=3), bronchopulmonary dysplasia 10% (n=3), foreign body aspiration 7% (n=2), aspiration secondary to gastric volvulus 3% (n=1), bronchogenic cyst 3% (n=1), bronchiectasis 3% (n= 1), dilated cardiomyopathy was detected in 3% (n=1) and hypereosinophilic syndrome in 3% (n=1) patients. Cystic fibrosis was detected in one of the 64 patients who underwent sweat testing, and the diagnosis was confirmed by mutation analysis. When all the cases were examined, it was observed that winter is 45% (n=34) of the attack season at the time of admission due to wheezing. However, there was no statistical difference between the groups. When the first attack times of the cases presenting due to wheezing attack are examined; In 59% (n=49) it was detected between 1-6 months and there was no significant difference between the groups. Again, when all the cases were examined, 28% (n=21) girls and 72% (n=55) boys were detected, and there was no statistically significant difference between the groups. In all cases, the maternal age was 59.6% (n=45) and under 29 years of age, while 40.8% (n=31) cases were 30 years of age or older and there was no statistical difference between the groups. When the cases were evaluated in terms of growth retardation, it was statistically significantly higher in the group with a specific diagnosis ($p<0.01$). According to the presence of smokers in the family, the smoking rates of the cases in the wheezing phenotypes group were statistically significantly higher than the cases in the specific diagnosed group. When total IgE levels were examined in the group containing wheezing phenotypes, a significant elevation was detected in cases with persistent atopic wheezing ($p<0.01$). In addition, the eosinophil percentage of the early transient wheezing group was significantly lower than that of the persistent atopic and non-atopic wheezing diagnostic groups ($p<0.01$); There was no significant difference between the persistent atopic group and the non-atopic group.

Conclusions: In terms of recurrent wheezing attack cases, being in winter, case age between 1-6 months, maternal age being under 29 years of age, gender being male was found to be significantly higher. Wheezing phenotype group demographic characteristics of the presence of smokers at home was significantly higher, while in the group of cases with specific diagnosis, growth retardation on physical examination was significantly higher it was found to be significantly higher.

Keywords: Recurrent wheezing, sociodemographic characteristics, growth retardation

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INTRODUCTION

Wheezing is a common presentation for pediatricians. In 1/3 of asthmatic children diagnosed before the age of five, the first symptoms occur before the age of two. Recurrent episodes of wheezing affect the child's diet, quality of life, growth, and development. Early recognition of persistent wheezing and correction of the underlying risk factors are important not only because of the morbidity and mortality it causes but also because of its long-term sequelae in adulthood (1). Clinically, wheezing is a physical examination finding suggestive of lower respiratory tract disease, characterised by small and medium-sized bronchial obstruction with rhonchi as a result of increased bronchial secretion. Chronic or recurrent wheezing may be caused by different primary aetiologies in different age groups. In general, asthma and reactive airway disease are the most common causes of wheezing (2).

Of the phenotypes typified according to the characteristics of the wheeze;

a) Transient early wheezing; the development of the respiratory tract is adversely affected during intrauterine life and babies are born with lower respiratory function compared to healthy babies. The main causes are smoking during pregnancy, low maternal age, low birth weight, and prematurity. Atopy and eosinophilic inflammation are absent (3). As these children grow, the dimensions of their airways change, and viral infections no longer cause wheezing (4). However, pulmonary function tests (PFTs) cannot catch up with their counterparts at any time. Although the prognosis seems very good due to the cessation of wheezing attacks at an early age (<3 years), the possibility of developing chronic obstructive pulmonary disease in adulthood is very high, especially if they also smoke.

b) Non-atopic wheeze (wheeze caused by viral infection); it has been observed that attacks in this phenotype are associated with viral infections. It is thought that the control of airway tone is altered during viral infection, leading to airway obstruction (4). It has not yet been clarified whether this physiological abnormality is congenital or occurs after a lower respiratory tract infection such as Respiratory Syncytial Virus (RSV) infection. This abnormality also decreases with advancing age, and statistical significance disappears when children reach the age of 13 years (4).

c) Persistent atopic wheeze (allergy-related atopic asthma); 60% of these children develop aeroallergen sensitisation by the age of 6 years. This may occur before or after the age of 3 years. The main difference between the two is that those who develop atopy before the age of 3 years have the worst lung function between the ages of 6 and 11 years. Other epidemiological studies of patients with persistent asthma suggest that symptoms begin in the first years of life.

Wheeze related to viral infection usually decreases over time and disappears around the age of 6 years. However, it has also been reported that it may continue in the form of a wheeze due to viral infection at school age, or it may develop into a multi-triggered wheeze or disappear at much later ages (5).

Wheeze is most common in infancy. The prevalence of wheezing in this age group varies from 4% to 32% (6). The reason for this high prevalence is related to the pulmonary mechanics of the airways at this age. Asthma, allergies, bronchiolitis, infections, congenital anomalies, foreign body aspiration, cystic fibrosis, gastro-oesophageal reflux, and tuberculosis (TBC) cause wheezing (6). Recurrent wheezing is defined as more than three episodes of wheezing or episodes of wheezing lasting more than 1 month (7). A diagnostic dilemma arises particularly in infants presenting with recurrent wheezing in the first 2 years of life. This situation is a source of concern for both the family and the healthcare team.

The first step in recurrent wheezing should be a history, careful physical examination, and then a chest X-ray. In the history, both individual and family history of atopy (such as atopic dermatitis, allergic rhinitis, and asthma) should be taken very carefully. Regarding the tests to be performed, skin tests are usually negative in very babies. RAST tests are also false negative. Viral infections are the most common cause of reactive airway disease. Environmental factors such as smoking and air pollution can also increase wheezing.

Hand hygiene, vaccination, and the use of masks are the most important ways of preventing and treating susceptible infants. Allergen-induced asthma is rare in this age group. It has been shown that wheezing, which begins early in life, is a heterogeneous condition, and recurrent airflow obstruction may be associated with different underlying mechanisms and even different diseases (7).

Because of this heterogeneity, treatment difficulties and failures are greater in older patients with asthma. In addition, atypical wheeze further complicates this disease. Even if they present with a typical wheeze, doctors are concerned about the diagnosis. As mentioned above, wheezing should be evaluated separately from recurrent lower respiratory tract infections in terms of both etiology and risk factors. Early initiation of studies on the etiology and good identification of risk factors are important for the prognosis of the disease.

In this study, it was aimed to compare phenomenological, familial, environmental causes and laboratory-imaging techniques between wheeze phenotype groups (Transient early wheeze group, Non-atopic wheeze group, and Persistent atopic wheeze patient group ageing from1 month-24 months) and the group with a specific diagnosis (Ventricular septal defect, Cystic fibrosis, Gastroesophageal reflux, etc.) causing recurrent wheeze.

MATERIALS AND METHODS

This was a retrospective cross-sectional study. Between January 2010 and November 2012 (a period of 35 months), 76 cases (7.8%) with three or more wheezing episodes or wheezing for more than 1 month or recurrent wheezing between 1 and 24 months of age were selected from 970 patients who were hospitalised in our hospital

for wheezing. Socioeconomic and demographic characteristics, risk factors, etiology, diagnosis, and ancillary diagnostic methods were obtained and evaluated both from the registered files and by contacting the families by telephone **(Table 1).**

Table 1. 26 Questions recorded for information on the case history, sociodemographic characteristics, and physical examination findings

a) Analysis of history (anamnesis)

Age at the time of application…
Gender…
Birth weight, Birth method, Birth week…
What was the complaint during the admission?
a) Cough b) Wheeze c) Fever d) Foreign body aspiration
Is the wheezing attack season at the time of application?
Age at first wheezing attack…
Total number of wheezing attacks…
Did the mother use assisted pregnancy methods during the prenatal period?
Is there a family history of atopy or allergic disease?

b) Sociodemographic characteristics

Is there a bottle feeding method used?
How many people live in a family house?
How many siblings go to school or nursery?
What floor is the house on?
What is the house heated with?
Is there humidity in the house?
Are there pets at home?
Is there anyone smoking at home?
Is there anyone in your family with chronic lung disease or allergic disease?
Mother's education level? a) Pre-high school? b) High school and beyond?

c) Review of the Physical Examination

Are there any rales on the physical examination?
Is expiring length present on physical examination?
Is there intercostal retraction on the physical examination?
Is there tachypnoea on the physical examination?
Are there signs of upper respiratory tract infection on physical examination?
Is there any growth and developmental delay in the physical examination?

The inclusion criteria were as follows:

1. At least three episodes of wheezing or wheezing persisting for more than 1 month

2. Being between 1 and 24 months old

3. No known medical condition (neuromuscular disease, congenital heart disease, etc.) that could cause recurrent wheezing.

Patients diagnosed with laboratory and imaging tests and found to have an aetiological factor were included in the specific diagnostic group. Patients in whom no aetiological factor for wheezing was found were included in the wheezing phenotype group.

Because our study was a retrospective cross-sectional study, ethics committee approval was not required.

RESULTS

Of the 970 patients aged 1-24 months admitted to our hospital for wheezing, 76 (7.8%) had three or more episodes of wheezing or had a wheeze lasting more than 1 month and had recurrent wheeze. The first group consisted of n = 29 (38%) patients with a specific diagnosis. In the second group, early transient wheeze was 15.7% (n=12), persistent atopic wheeze was 21% (n=16) and non-atopic wheeze was 25% (n=19).

The mean number of wheeze episodes for all subjects was 3.66±0.92 per year. No statistically significant difference was found between the specific diagnosis group and the wheeze phenotype groups (p>0.05). When the seasons of the attack were examined for all subjects at the time of presentation for wheeze, 23.7% (n=18) were in spring, 11.8% (n=9) in summer, 19.7% (n=15) in autumn and 44.7% (n=34) in winter. When the age of the first attack of all cases was analysed, it was observed that 59.2% (n=49) were between 1-6 months, 19.7% (n=15) were between 7-12 months and 21.1% (n=16) were 13 months or more **(Table 2).**

Table 2. Evaluations Regarding Wheezing

		All Cases		Wheezing Phenotypes		Specific Diagnose		*p*
		Mean±SD		Mean ±SD		Mean ±SD		
Number of Wheezing Attacks		3,66±0,92		3,77±1,03		3,47±0,66		[a]***0,233***
		n	%	**n**	**%**	**n**	**%**	
Wheezing Attack Season	**Spring**	18	23,7	13	27,7	5	17,2	[c]***0,521***
	Summer	9	11,8	4	8,5	5	17,2	
	Autumn	15	19,7	10	21,3	5	17,2	
	Winter	34	44,7	20	42,6	14	48,3	
Age of the First Wheezing Attack	**0-6 Month**	45	59,2	26	55,3	19	65,5	[c]***0,675***
	7-12 Month	15	19,7	10	21,3	5	17,2	
	≥ 13 month	16	21,1	11	23,4	5	17,2	

When the seasons of the attack were examined for all subjects at the time of presentation for wheeze, 23.7% (n=18) were in spring, 11.8% (n=9) in summer, 19.7% (n=15) in autumn and 44.7% (n=34) in winter. In the wheezing phenotype group, 27.7% (n=13) were in spring, 8.5% (n=4) in summer, 21.3% (n=10) in autumn and 42.6% (n=20) in winter. In the specific diagnosis group, 17.2% (n=5) of the cases were in spring, 17.2% (n=5) in summer, 17.2% (n=5) in autumn and 48.3% (n=14) in winter. No statistically significant difference was found between the groups (p>0.05). These data are presented in **Table 2**.

When the ages of the first attack of all subjects were analysed, it was observed that 59.2% (n=49) were between 1-6 months, 19.7% (n=15) were between 7-12 months and 21.1% (n=16) were 13 months and older. In the wheeze phenotypes group,

55.3% (n=26) of the cases were between 1 and 6 months, 21.3% (n=10) between 7 and 12 months and 23.4% (n=11) at 13 months and above, while 65.5% (n=19) of the cases in the specific diagnosis group were between 1 and 6 months, 17.2% (n=5) between 7 and 12 months and 17.2% (n=5) at 13 months and above. No statistically significant difference was found between the groups (p>0.05). These data are shown in **Table 2.**

The mean age of all subjects was 11.71±6.05 months, the mean age of subjects in the wheeze phenotype group was 12.68±5.92 months and the mean age of subjects in the specific diagnosis group was 10.14±6.03 months. No statistically significant difference was found between the groups (p>0.05). These data are presented in **Table 3.**

The mean gestational age of all subjects was 37.61±3.23 weeks, the mean gestational age of subjects in the wheeze phenotype group was 37.30±3.07 weeks and the mean gestational age of subjects in the specific diagnosis group was 38.10±3.48 weeks. No statistically significant difference was found between the groups (p>0.05). These data are presented in **Table 3.**

The mean birth weight of all subjects was 2890.46±780.29 g, the mean birth weight of subjects in the wheezing phenotype group was 2858.83±770.51 g and the mean birth weight of subjects in the specific diagnosis group was 2941.72±806.93 g. No statistically significant difference was found between the groups (p>0.05). These data are presented in **Table 3.**

When analysing the mode of delivery of the cases, 57.9% (n=44) of all cases were C/S, 42.1% (n=32) were Normal Spontaneous Birth (NSB), 66% (n=31) of the cases in the wheezing phenotype group were C/S, 34% (n=16) were NSB and 44.8% (n=13) of the cases in the specific diagnosis group were C/S, 55.2% (n=16) were NSB. There was no statistically significant difference between the groups (p>0.05). These data are presented in **Table 3.**

In all cases, 27.6% (n=21) were female and 72.4% (n=55) were male. In the wheeze phenotype group, 29.8% (n=14) were female and 70.2% (n=33) were male, and in the specific diagnosis group, 24.1% (n=7) were female and 75.9% (n=22) were male. No statistically significant difference was found between the groups (p>0.05). These data are presented in **Table 3.**

While 22.4% (n=17) of all subjects were born at or before 37 weeks, 77.6% (n=55) were born after 37 weeks. In the wheeze phenotype group, while 27.7% (n=13) were born at or before 37 weeks and 72.3% (n=34) were born after 37 weeks, in the specific diagnosis group, 13.8% (n=4) were born at or before 37 weeks and 86.2% (n=25) were born after 37 weeks. There was no statistically significant difference between the groups (p>0.05). These data are presented in **Table 3.**

When the cases were analysed according to bottle use, it was found that all cases were 47.4% (n=36). While 53.2% (n=25) of the subjects in the wheeze phenotypes group had bottle use, 37.9% (n=11) of the subjects in the specific diagnosis group had bottle use. No statistically significant difference was found between the groups (p>0.05). These data are shown in **Table 4.**

When analysing the number of persons in the family, 56.6% (n=43) of the subjects had a family of 3-4 persons, 22.3% (n=17) had a family of 5 persons and 21.1% (n=16) had a family of 6 or more persons. No statistically significant difference was found between the wheeze phenotypes and the specific diagnosis group (p>0.05). These data are presented in **Table 4**.

When analysing the presence of a smoker in the family, smoking was observed in 53.9% (n=41) of the cases. Smoking was observed in 63.8% (n=30) of the families of subjects in the wheeze phenotype group and 37.9% (n=11) of the families of subjects in the specific diagnosis group. A statistically significant difference was found between the groups (p<0.05). Smoking rates were significantly higher in subjects in the wheezing phenotype group than in those in the specific diagnostic group. These data are presented in **Table 4.**

When analysed according to the heating types of the cases, it was observed that 51.3% (n=39) of the houses were heated with natural gas, 30.3% (n=23) with natural gas stoves, and 18.4% (n=14) with wood stoves. There was no statistically significant difference between the groups according to the heating methods (p>0.05). These data are shown in **Table 4.**

Table 3. Evaluation of Birth Anamnesis Features

		All Cases		Wheezing Phenotypes		Specific Diagnose		p
		Mean ±SD		Mean ±SD		Mean ±SD		
Age (month)		11,71±6,05		12,68±5,92		10,14±6,03		***[a]0,075***
Age of Gestation (week)		37,61±3,23		37,30±3,07		38,10±3,48		***[a]0,294***
Birth Weight (gr)		2890,46±780,29		2858,83±770,51		2941,72±806,93		***[a]0,656***
The type of birth	**C/S**	n=44	% 57,9	n=31	% 66	n= 13	% 44,8	
	NSD	n=32	% 42,1	n=16	% 34	n=16	% 55	
Gender	**Female**	n=21	% 27,6	n=14	% 29,8	n = 7	% 24,1	***[b]0,786***
	Male	n=55	%72	33	%70	n=22	%75,9	
Prematurity	**≤ 37 week**	n=17	%22,4	n=13	%27,7	n=4	%13,8	***[b]0,260***
	>37 week	n=59	%77	n=34	%72,3	n=25	%86	

NSD: normal spontaneous delivery, a Student-T-test, b Yates Continuity Correction

When a family history of lung disease (pulmonary tuberculosis) and allergic disease (family history of asthma) was analysed, 21.1% (n=16) of the families of all subjects had lung disease, whereas 78.9% (n=60) did not. No statistically significant difference was found between the groups according to the family history of lung disease (p>0.05). These data are shown in Table 4. However, the presence of asthma in the family history of 50% (n=8) of the subjects diagnosed with persistent atopic wheeze was found to be significantly higher in the wheeze phenotype group.

When analysing the presence of dampness in the houses of the cases, it was found that all cases had dampness. While 65.8% (n=50) had no dampness, 34.2% (n=26) had dampness. While no statistically significant difference was found between the groups according to the presence of dampness in the home (p>0.05), the high rate of dampness in the wheezing phenotype group was notable. These data are presented in **Table 4.**

When analysing the number of siblings attending school, it was found that in all cases 39.5% (n=30) had no siblings attending

Table 4. Evaluation of the Sociodemographic Characteristics

		All Cases	Wheezing Phenotypes	Specific Diagnose	*p*
		n (%)	n (%)	n (%)	
Baby Bottle Use	**No**	40 (%52,6)	22 (%46,8)	18 (%62,1)	[b]***0,290***
	Yes	36 (%47,4)	25 (%53,2)	11 (%37,9)	
Number of people in the family	**3-4 İndividual**	43 (%56,6)	29 (%61,7)	14 (%48,3)	[b]***0,363***
	5 İndividual	17 (%22,3)	8 (%17,0)	9 (%31,0)	[b]***0,254***
	≥ 6 İndividual	16 (%21,1)	10 (%21,3)	6 (%20,7)	[b]***1,000***
Presence of Smokers in the Family	**No**	35 (%46,1)	17 (%36,2)	18 (%62,1)	[b]***0,050****
	Yes	41 (%53,9)	30 (%63,8)	11 (%37,9)	
Warm-up method	**Natural gas**	39 (%51,3)	23 (%48,9)	16 (%55,2)	
	Natural Gas Stove	23 (%30,3)	13 (%27,7)	10 (%34,5)	[c]***0,355***
	Stove	14 (%18,4)	11 (%23,4)	3 (%10,3)	
Lung Disease in the Family-Allergic disease	**No**	60 (%78,9)	36 (%76,6)	24 (%82,8)	[b]***0,726***
	Yes	16 (%21,1)	11 (%23,4)	5 (%17,2)	
Presence of Moisture in the House	**No**	50 (%65,8)	27 (%57,4)	23 (%79,3)	[b]***0,089***
	Yes	26 (%34,2)	20 (%42,6)	6 (%20,7)	
Number of Siblings Going to School	**No**	30 (%39,5)	18 (%38,3)	12 (%41,4)	
	1 Brother	29 (%38,2)	18 (%38,3)	11 (%37,9)	[c]***0,950***
	≥2				
	Brothers	17 (%22,4)	11 (%23,4)	6 (%20,7)	

Table 5: Evaluation of Maternal Characteristics

		All Cases		Wheezing Phenotypes		Specific Diagnose		*p*
		n	%	n	%	n	%	
Mother Age	**< 20 years of age**	6	7,9	4	8,5	2	6,9	
	20-29 years of age	39	51,3	24	51,1	15	51,7	[c]***0,968***
	≥30 years of age	31	40,8	19	40,4	12	41,4	
Mother Age	**≤ 29 years of age**	45	59,2	28	59,6	17	58,6	
	> 29 years of age	31	40,8	19	40,4	12	41,4	[b]***1,000***
	Primary school	42	55,3	26	55,3	16	55,2	
Mother Education	**High School**	29	38,2	16	34	13	44,8	[c]***0,163***
	University	5	6,6	5	10,6	0	0	
Mother Education	**Under high school**	42	55,3	26	55,3	16	55,2	[b]***1,000***
	High School and Above	34	44,7	21	44,7	13	44,8	

[b]Yates Continuity Correction, [c]Pearson Chi-Square

school, 38.2% (n=29) had one sibling attending school and 22.4% (n=17) had two or more siblings.

No statistically significant difference was found between the groups according to the number of siblings attending school (p>0.05). These data are presented in **Table 4**.

The maternal age was less than 20 years in 7.9% (n=6), between 20 and 29 years in 51.3% (n=39), and 30 years or more in 40.8% (n=31) of all cases. In the wheeze phenotype group, 8.5% (n=4) had a maternal age less than 20 years, 51.1% (n=24) had a maternal age between 20 and 29 years, and 40.4% (n=19) had a maternal age of 30 years or more. In the specific diagnosis group, maternal age was less than 20 years in 6.9% (n=2), between 20 and 29 years in 51.7% (n=15), and 30 years or more in 41.4% (n=12). No statistically significant difference was found between the groups (p>0.05). These data are presented in **Table 5.**

No statistically significant difference was found between the maternal age of the wheeze phenotype group and the specific diagnosis group (p>0.05). These data are presented in **Table 5.**

The maternal education of 55.3% (n=42) of all subjects was primary school, 38.2% (n=29) high school, and 6.6% (n=5) university. In the wheeze phenotype group, 55.3% (n=26) had primary education, 34% (n=16) had high school education and 10.6% (n=5) had a university education. In the specific diagnosis group, 55.2% (n=16) had primary education and 44.8% (n=13) had high school education. No statistically significant difference was found between the groups (p>0.05). These data are presented in **Table 5.**

No statistically significant difference was found between the maternal education level of the wheeze phenotype group and the specific diagnosis group (p>0.05). These data are presented in **Table 5.**

Cough was observed in 50% (n=38) of all subjects. Cough was observed in 48.9% (n=23) of subjects in the wheeze phenotype group and 51.7% (n=15) of subjects in the specific diagnostic group. There was no statistically significant difference between the groups (p>0.05). Wheeze was observed in 64.5% (n=49) of all cases. Wheeze was observed in 59.6% (n=28) of subjects in the wheeze phenotype group and 72.4% (n=21) of subjects in the specific diagnostic group. There was no statistically significant difference between the groups (p>0.05).

Fever was observed in 36.8% (n=28) of all cases. In 38.3% (n=18) of the wheeze phenotype group and 38.3% (n=18) of the specific diagnostic group. Fever was observed in 34,5% (n=10). There was no statistically significant difference between the groups (p>0.05).

Atopy was observed in 15.8% (n=12) of all subjects. In 19.1% (n=9) of the wheeze phenotypes group, in 19.1% (n=9) of the subjects in the specific diagnostic group

Atopy was observed in 10.3% (n=3). No statistically significant difference was found between the groups (p>0.05). The lack of difference in terms of atopy may be because atopy requires at least 12-15 months of sensitisation and the high number of cases with early wheezing in the first 2 years of age group. There was no statistically significant difference between the

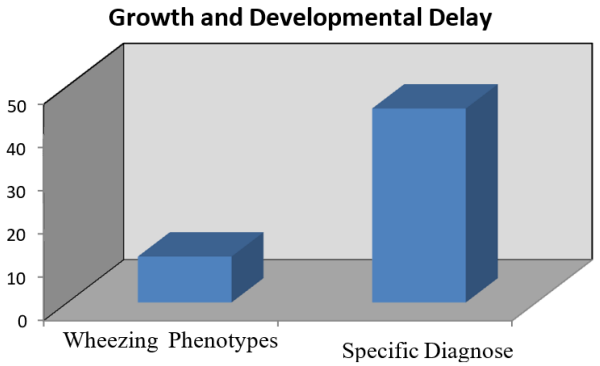

Figure 1: Distribution of Growth and Developmental Delay Rates.

Table 6. Evaluation of immunoglobulin Levels According to Groups

		All Cases		Wheezing Phenotypes		Specific Diagnose		[b]p
		n	%	n	%	n	%	
IgA	**Normal**	67	90,5	45	95,7	22	81,5	***0,108***
	Low	3	4,1	2	4,3	1	3,7	***1,000***
Total IgE	**Normal**	51	74,3	31	66	24	88,9	***0,050****
	Above	19	25,7	16	34	3	11,1	
IgM	**Normal**	64	86,5	43	91,5	21	77,8	***0,191***
	Low	2	2,7	1	2,1	1	3,7	***1,000***
	Above	8	10,8	3	6,4	5	18,5	***0,219***
IgG	**Normal**	65	87,8	39	83	26	96,3	***0,158***
	Low	6	8,1	6	12,8	0	0	***0,135***
	Above	3	4,1	2	4,3	1	3,7	***1,000***

[b]Yates Continuity Correction, p<0,05*

groups for the presence of rales, expiratory length, intercostal retraction, tachypnoea, and viral infection (p>0.05).

A statistically significant difference was found between the groups according to growth and developmental delay (p<0.01). The rate of growth and developmental delay observed in the specific diagnosis group was significantly higher than that observed in the wheeze phenotypes group. This is shown in **Figure 1.**

No statistically significant difference was found between the groups for WBC and CRP levels (p>0.05).

When the subjects were analysed according to IgA levels, no statistically significant difference was found between the normal and low levels groups (p>0.05). These data are presented in **Table 6.**

When analysed according to the total IgE measurement values of the subjects, the IgE elevation in the wheezing phenotype group was found to be statistically borderline significantly higher than in the subjects with specific diagnosis (p<0.05). These data are presented in **Table 6.**

When analysed according to the IgM measurement values of the cases; no statistically significant difference was found between the groups according to the normal, low, and high measurement values (p>0.05). These data are shown in **Table 6**.

When the subjects were analysed according to IgG levels, no statistically significant difference was found between the groups according to normal, low, and high levels (p>0.05). These data are presented in **Table 6.**

When total IgE was analysed according to the case status, the mean values were 206.00±134.21 U/ml for persistent atopic wheeze, 16.61±16.754 U/ml for non-atopic wheeze and 17.18±16.256 U/ml for early transient wheeze. A statistically significant difference was found between the diagnostic groups (p<0.01). The persistent atopic diagnostic group was statistically significantly higher than the other diagnostic groups. These data are shown in **Figure 2.**

When the eosinophil percentage of the patients was analysed according to the presentation status, it was 3.59±2.10%

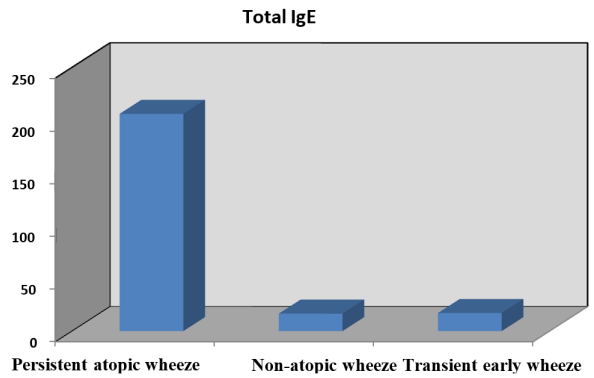

Figure 2: Total IgE distribution of the wheezing phenotype groups.

for persistent atopic diagnosis, 2.56±1.44% for non-atopic diagnosis, and 0.73±0.51% for early transient wheeze diagnosis. A statistically significant difference was found between the diagnostic groups (p<0.01). The eosinophil percentage in the group diagnosed with early transient wheeze was significantly lower than that in the groups diagnosed with persistent atopic and non-atopic wheeze (p<0.01); no significant difference was found between the persistent atopic group and the non-atopic group (p>0.05).

When the chest radiograph parameters of the cases were analysed, 2.7% (n=2) of all cases had a difference in aeration, 29.3% (n=22) had excess aeration, 25.3% (n=19) had infiltration, 16% (n=12) had perihilar infiltration and 26.7% (n=20) were normal, whereas 36.2% (n=17) of the wheeze phenotype group had excess aeration, 19. 1% (n=9) had infiltration, 10.6% (n=5) had perihilar infiltration and 34% (n=16) were normal, whereas in the specific diagnosis group, 7.1% (n=2) had ventilation difference, 17.9% (n=5) had infiltration, 14.3% (n=4) had perihilar infiltration and 25% (n=7) were normal. No statistically significant difference was found between the groups according to chest radiograph parameters (p>0.05). These data are shown in **Table 7.**

When analysing the chest CT results, a statistically significant difference was found between the rates of subjects with normal chest CT results according to the groups (p<0.05). Normal chest CT results were statistically significantly higher in the wheeze phenotype group than in the specific diagnostic group. No statistically significant difference was found between the distributions according to the chest CT results (p>0.05). These data are presented in **Table 7.**

A statistically significant difference was found between the distribution of esophagus-stomach-duodenal (ESD) radiographs according to groups (p<0.05). The detection rate of gastro-oesophageal reflux in ESD was significantly higher in patients with specific diagnoses. These data are shown in **Table 7**.

There was a statistically significant difference between the pH metre distributions according to the groups (p<0.05). The rate of gastro-esophageal reflux detection in the pH metre was found to be significantly higher in cases with specific diagnoses. These data are shown in Table 7.

Videofluoroscopy was used in the diagnosis of 5 cases in the specific diagnosis group, and oropharyngeal aspiration was detected in 4 cases. These data are shown in **Table 7**.

There was no statistically significant difference between the echocardiography (ECHO) distributions according to the groups (p>0.05). However, it is noteworthy that all 4 cases with abnormalities in ECHO were in the specific diagnostic group. Secundum ASD (n=2), Bicuspid aorta (n=1), and Dilated cardiomyopathy (n=1) were detected in the patients with pathological ECHO results. These data are shown in **Table 7.**

Alpha-1 antitrypsin results also did not show any statistically significant difference between groups (p>0.05) Cow's milk

Table 7. Evaluation of Chest X-ray, Thorax CT, ESD graph, ECHO, Sweat Test, pHmeter Results

	All Cases		Wheezing Phenotype	Specific Diagnose	*b*
	n	%	n (%)	n (%)	
Chest X-Ray					
Difference in aeration	2	2,7	0 (%0)	2 (%7,1)	***0,264***
Increased aeration	22	29,3	17 (%36,2)	5 (%17,9)	***0,155***
Infiltration	19	25,3	9 (%19,1)	10 (%35,7)	***0,186***
Perihilar infiltration	12	16,0	5 (%10,6)	4 (%14,3)	***0,918***
Normal	20	26,7	16 (%34,0)	7 (%25,0)	*0,574*
Thorax CT					
Normal	12	61,3	8 (%72,7)	4 (%20,0)	***0,012****
Mosaic Pattern	2	6,5	0 (%0,0)	2 (%10,0)	***0,749***
Mass	1	3,2	0 (%0,0)	1 (%5,0)	***1,000***
Interstitial infiltration	2	6,5	0(%0,0)	2 (%10,0)	***0,749***
Ground Glass Image	7	22,6	1 (%9,1)	6 (%30,0)	***0,377***
Bronchiectasis	1	3,2	0 (%0,0)	1 (%5,0)	***1,000***
Atelectasis	5	16,1	3 (%27,3)	2 (%10,0)	***0,459***
Consolidation	4	12,9	2 (%18,2)	2 (%10,0)	***0,928***
ESD graph					
Normal	10	52,6	7 (%100,0)	3 (%25,0)	***0,007****
Reflux	9	47,4	0 (%0,0)	9 (%75,0)	
ECO					
Normal	58	95,1	38 (%100,0)	20 (%87,0)	***0,094***
Abnormal	3	4,9	0 (%0,0)	3 (%13,0)	
Sweat test					
< 40	53	82,8	33 (%82,5)	20 (%83,3)	***1,000***
40–60	10	15,6	7 (%17,5)	3 (%12,5)	***0,859***
> 60	1	1,6	0 (%0,0)	1 (%4,2)	***0,795***
Phmetre					
Normal	19	73,1	17 (%100,0)	2 (%22,2)	***0,001****
Reflux	7	26,9	0 (%0,0)	7 (%77,8)	

[b]Yates Continuity Correction, p<0,05*, p<0,001**

protein IgE results did not show any statistically significant difference between groups (p>0.05). However, cow's milk protein-specific IgE levels were found to be significantly high in 2 cases in the wheezing phenotype group.

The sweat test results also did not show any statistically significant difference between groups (p>0.05). These data are shown in **Table 7.**

PPD was performed on all cases and PPD positivity was detected in one case, and there was no statistically significant difference between the groups (p>0.05).

DISCUSSION

Wheezing is a multifactorial symptom with different causes for each age group and is common in children. Atopy, genetic causes such as family history, frequent viral infections, and environmental causes such as exposure to cigarette smoke are risk factors for chronic wheezing. Despite many studies, it is not yet clear why the same environmental factors do not cause the same symptoms even in siblings. At least 30% of children experience a wheezing attack before the age of 3 and 50% before the age of 6. In persistent wheezing, loss of lung function begins after the first year, becomes apparent at the age of 6, and continues until adulthood (8). Twenty-five percent of children under one year of age and 13% of children aged 1 to 2 years develop respiratory tract infections, and half of these cases involve wheezing (9). There is strong epidemiological evidence that approximately two-thirds of wheezing episodes during the early school years are due to viral infection (9). Viruses, primarily Respiratory Syncytial Virus (RSV) and less frequently Adenovirus and Parainfluenza viruses, generally

cause wheezing attacks in the first 3 years of life. Our research has determined that wheezing attacks are more intense in the winter months. Since these viruses are more common in the winter months, it is likely that the cause of wheezing is mostly viral infection or triggered by viral infection.

The most important factors in the evaluation of a wheezy child are the age of onset of wheezing, whether it is recurrent or chronic, the presence of symptoms such as fever, developmental delay, chest deformity, clubbing, familial allergy history, and whether there is a response to bronchodilator treatment (10). Thus, etiology should be investigated within the framework of a specific algorithm. A careful history and physical examination can detect diseases such as foreign body aspiration, cystic fibrosis, gastroesophageal reflux disease, viral pneumonia, or pulmonary tuberculosis (11). Anatomical defects, congenital heart disease, laryngo-tracheo-malacia, and diaphragmatic hernia should be investigated for early medical and surgical treatment.

When the time of the first wheezing attacks of children with wheezing is considered, it is seen that it is mostly in the 0-6 months period. The fact that the largest patient group in our study was 1-6 month-old babies (59.2%) can be explained by anatomical reasons and the inadequate development of the immune system. Inal et al. (10) also determined the first attack age as 0-6 months period in their study. Our results are parallel to the results of this study. In addition to the local effects of viral infection in the small respiratory tract, many anatomical factors contribute to the narrowing of the respiratory tract in infants. The narrowness of the peripheral respiratory tracts in children causes them to become easily obstructed. In infants, many mucous glands are secreted in the respiratory tract, and the respiratory tract mucosa is looser. Thus, submucosal edema occurs more easily. However, the foramina of Kohn are fewer in number and less developed in the infant lung. Therefore, collateral ventilation is not as effective as in adults. Excessive ventilation and atelectasis develop more easily. In our study, atelectasis was detected in 16.1% (n=5) of the cases in which thoracic CT was performed, 2 of the cases were 5 months old, 1 case was 3 months old, 1 case was 4 months old, and 1 case was 9 months old. The risk of wheezing attacks increases in premature babies and babies with a birth weight of less than 2,500 grammes. In a study conducted in our country, wheezy children were investigated in terms of birth weight, and no significant difference was found between wheezy children and healthy children (12). Sherriff et al. tried to determine the risk factors in wheezy children and determined only low birth weight (<2,500 grammes) as a definite risk factor (13).

In our study, no significant difference was found in the specific diagnosis group and the wheezing phenotype group with birth weight and premature birth. The results of studies investigating gender as a risk factor contain differences. While wheezing was determined as a definite risk factor for the male gender in one study (13), no connection was found between the male gender and wheezing in another study (14). In our study, wheezing was found to be significantly higher in males in both groups, but no statistical difference was found between the groups.

It is thought that the risk factors that determine the tendency to wheeze and asthma may be effective at an early age and perhaps even in the intrauterine environment. These factors include fetal nutrition (15), gestational age (16), exposure to cigarette smoke (17), environmental air pollution (3), postnatal nutrition, breastfeeding, family size, maternal age, socioeconomic status, and exposure to allergens (18-20). Exposure to passive smoking is a risk factor for infants, especially if the mother smokes. In one study, the relationship between prenatal and postnatal familial smoking and wheezy infants was examined in two different populations. As a result of this study, a significant relationship was found between both maternal smoking during pregnancy and exposure to passive smoking and wheezy infants, and it was suggested that the dose-dependent effects of prenatal and postnatal exposure of infants to tobacco smoke may be important (21). Family smoking, especially maternal smoking, increases the risk of wheezing symptoms and lower respiratory tract diseases (22). Another study has shown that wheezy children are more exposed to passive smoking than healthy children (23). In 496 cases with recurrent wheezing attacks who were followed up to 14 months of age, maternal smoking, especially in the first 2-3 months, was found to be a risk factor (24).

In this study, because the number of mothers who smoked during pregnancy was low (only the wheezing phenotype group (n=2)), no comparison was made. When the rates of smoking in the family were examined, the wheezing phenotype group was found to be significantly higher than the specific diagnostic group.

While breastfeeding is thought to reduce wheezing attacks in children, there is still no evidence-level data on its protective effect against persistent asthma. Due to ethical concerns, the number of studies on the subject is almost non-existent. In addition, the World Health Organisation also recommends that all children with and without a risk of allergy be breastfed for the first 6 months to prevent malnutrition, which is still common worldwide. A study in China has shown that formula feeding contributes to respiratory illness requiring hospitalisation in the first 18 months (18). It was observed that the risk of wheezing was higher in children living in houses heated with wood (25). In our study, no significant difference was found between formula feeding and home heating devices in both groups.

Children with school-age siblings and infants in nurseries are at a high risk of experiencing attacks (25). However, in terms of the development of atopic diseases, many studies in Western countries have shown an inverse relationship between the number of siblings and atopic diseases, and it has been suggested that increasing the number of siblings has a protective effect by increasing the risk of infection. However, while some studies have identified the presence of a sibling as a risk factor, others have not been able to identify a relationship between wheezing and the presence of a sibling. Thus, contrary

to previous publications, new studies have found early viral respiratory tract infections to be protective against asthma, and a clear consensus has not yet been reached on this issue (26). In our study, no significant difference was found in terms of viral infection in both groups. Strachan and colleagues determined that humidity in bedrooms is an important risk factor for wheezing (27). In our study, no statistically significant difference was found between the groups according to the presence of humidity in the house, but the high humidity rate in the wheezing phenotype group was remarkable. Humidity can of course lead to mould formation in the house over time, which can lead to mould allergy in the future. However, considering the average age of the group we examined (<2 years), it seems a bit early for this. For this, it is necessary to be approximately 12-15 months older.

Tachypnea, retraction, and prolonged expiration are common findings on physical examination; cyanosis and nasal flaring may also be seen depending on the severity of the disease (28). The expiratory length was found to be 97%, rales 64%, tachypnea 27%, and intercostal retraction 23%, and no significant difference was found between the groups. Growth and developmental delay were found to be significantly higher in the specific diagnosis group than in the wheezing phenotype group. This is an expected result and should be considered natural.

There are many studies investigating the role of immunoglobulin levels in wheezy infants, especially considering the susceptibility to respiratory tract infections and immune deficiency. While some studies could not find any relationship between immunoglobulin levels and wheezing (29), Öner et al. found low IgG3 and/or IgG4 levels and high IgE levels in their study and concluded that immunoglobulins may play a role in the pathogenesis of childhood wheezing (30).

Independent of allergen-specific reactivity, studies in children and adults have reported a close relationship between total serum IgE levels and the prevalence of asthma. A prospective population study showed that children who were sensitised early and had persistent wheezing had high IgE levels throughout childhood. Consequently, it may be useful to know in which children IgE is effective in determining disease risk. When laboratory findings were evaluated in our study, it was observed that both total IgE and total eosinophil percentage were significantly higher in the persistent atopic cases of the wheezing phenotype group compared with the cases of other wheezing phenotype groups. In addition, a partial IgA decrease was detected in 3 cases, a total IgE increase was detected in 19 cases, an IgM decrease was detected in 2 cases, and an IgG decrease was detected in 6 cases. It was observed that immunoglobulin levels increased in the follow-up of cases with hypogammaglobulinemia. These are likely to be either physiological or transient hypogammaglobulinemias, at which time the infection has either been prolonged or relapsed.

In a wheezy child, increased ventilation in both lungs (more than seven ribs ventilation, ribs becoming parallel, diaphragm flattening, reduction in the mediastinum and heart area, increase in the retrosternal space on the lateral radiograph), peribronchial infiltrates and atelectasis can be seen radiologically. Patchy density increase can also develop due to atelectasis and secondary bacterial infection (28). In all our cases, it was observed that 2.7% (n=2) had a difference in ventilation, 29.3% (n=22) had excess ventilation, 25.3% (n=19) had infiltration, 16% (n=12) had perihilar infiltration, and 26.7% (n=20) were normal. No statistically significant difference was found between the groups in terms of chest X-ray findings (p>0.05). When thoracic CT results were examined, normal (%61), ground-glass appearance (%22.6), atelectasis (%16.1), consolidation (%12.9), mosaic pattern (%6.5), interstitial infiltration (%6.5), bronchiectasis (%3.2), and mass (%3.2) were detected in all cases. The normality of the thorax CT results of the cases in the wheezing phenotype group was statistically significantly higher than the cases in the specific diagnostic group. No statistically significant difference was found between the distributions according to the thorax CT results (p>0.05). The advanced examinations (PPD, sweat test, pH metre) of the patient with bronchiectasis were found to be normal. A case with a mass was taken to surgery, and the mass was found to be a bronchogenic cyst because of pathological examination. Gastroesophageal reflux disease (GERD) causes recurrent cough, wheezing, and aspiration pneumonia, especially in the first years of life, and therefore constitutes an important problem in the differential diagnosis of wheezy infants. Wheezing after feeding, frequent vomiting, prominent nocturnal symptoms, and worsening with bronchodilator treatment should be particularly alert for GERD. The most reliable method for diagnosing GERD is to record the pH changes in the lower esophagus with a pH metre for 24 h (31). In one study, 40 patients with respiratory symptoms were investigated for GERD, and GERD was detected in 35% of the patients (32). It was observed that there was a significant improvement in the respiratory symptoms of the patients who were diagnosed with GERD and started on anti-reflux treatment. In another study, reflux scintigraphy was performed on 43 of 110 children with wheezing attacks, and GERD was found to be positive in 24 patients (12). In our study, 25% (n=19) of the cases underwent Esophagus Stomach Duodenum (ESD) graphs and GERD was detected in 11% (n=10). pH metre was used in 34% (n=26) of the cases and GERD was detected in 9% (n=7). In total, GERD was detected in 10 cases with ESD and 7 cases with pH metre. In 2 of the cases, GERD was detected with orotracheal aspiration, 2 with aspiration pneumonia, 1 with gastric volvulus, and 1 with hypogammaglobulinemia. Tuberculosis continues to be a major problem all over the world, especially in developing countries and is included in the etiology of patients presenting with wheezing (33). In one study, a patient who was hospitalised with a preliminary diagnosis of a foreign body due to short-term wheezing and chest X-ray findings was reported to have tuberculous lymphadenitis after histopathological and microbiological examination of a mass that caused extraluminal compression of the airways as a result of bronchoscopy (34). In our study, the PPD test was found to be positive in 1 case, but the case had

no history of contact, chest X-ray was normal, thorax CT was normal, the Quantiferon test was negative, ARB (Acid-Resistant Bacillus) was negative in fasting gastric juice and no growth was detected in mycobacteria culture. The most common food allergy in infancy is cow's milk allergy. In developed countries, the incidence in infants under 2 years of age is around 2%. Almost half of them are IgE-dependent, and the other half are not. It occurs not only with direct cow's milk but also with the ready-made formula. The allergic reaction starts within the first 4 weeks after starting the ready-made formula. The vast majority recover before the age of 3 (35). In our study, a cow's milk IgE test was performed in 90% (n=68) cases and cow's milk-specific IgE was detected as positive in two cases in the wheezing phenotype group. The formula they were using was stopped and the amino acid-based formula was started. Wheezing due to cardiovascular anomalies occurs in the first weeks of life. It is heard both inspiratory and expiratory during cardiac auscultation. Wheezing due to the right main bronchus, abnormal left pulmonary artery compression, and double aortic arch may occur with difficulty swallowing (2). However, cardiac causes leading to heart failure may cause recurrent wheezing. In our study, ECHO was performed in 86% (n=65) of the patients and dilated cardiomyopathy was detected in 1 case, bicuspid aortic valve in 1 case, and secundum ASD in 2 cases.

Hypereosinophilic syndrome, a rare cause of wheezing in children, is sometimes revealed by detecting eosinophilia during routine examinations. The diagnosis is made after excluding other conditions known to cause chronic eosinophilia (36). The patient in the specific diagnosis group diagnosed with hypereosinophilic syndrome had a history of hyperemic (macular) rash that started at the age of 6 months and then recurrent wheezing attacks. The eosinophil level was 13.2% (2.400/mm3) and the serum IgE level was 460 IU/ml at presentation. The diagnosis was made after excluding other causes of hypereosinophilia (intestinal parasitosis, hematological malignancy, hyper IgE syndrome, Churg-Strauss syndrome). It was thought that the asthma that developed in this patient could be related to the eosinophilic involvement of the airways. Flexible bronchoscopy is recommended to visualise the respiratory tract in cases presenting with recurrent wheezing when history, clinical, and laboratory findings do not lead to a possible diagnosis to elucidate the etiology or in cases with late or unresponsive response to treatment. Flexible bronchoscopy and BAL (bronchoalveolar lavage), which is a critical step in evaluating congenital anomalies of the larynx or bronchi, could be performed in 5 cases. Tracheomalacia with aspiration pneumonia was detected in 1 case, aspiration pneumonia in 1 case, foreign body aspiration in 2 cases, and the findings were normal in 1 case. In the virtual bronchoscopy experience from the literature, foreign body aspiration (FBA), sunflower, and fruit seeds were detected in some cases. While one of our cases had a history of FBA, no history of FBA was detected in the other. A sunflower seed was detected as a foreign body in one case and a fruit seed in one case.

In every case with recurrent wheezing attacks and where allergic/atopic asthma is not considered, other causes should be considered. Anatomical defects, congenital heart disease, laryngo-tracheomalacia, and diaphragmatic hernia should be investigated for early medical and surgical treatment. A careful history and physical examination can detect diseases such as FBA, cystic fibrosis, GERD, viral pneumonia, or pulmonary tuberculosis (11). Many studies have identified cystic fibrosis as the etiology of wheezy children and have shown that wheezing develops more frequently due to airway hyperreactivity (37). In addition, although the most common cause of wheezing is bronchial asthma when it occurs in the neonatal period and does not respond to bronchodilator treatment, a hereditary disease such as cystic fibrosis or a congenital anomaly should be considered first (38). In the study conducted by Çevik D et al., the sweat test results were found to be >60 mmol/L in 19 out of 69 patients (29%) (12). In our study, a sweat test was performed in 64 (84%) of the cases, and the sweat Cl was found to be <40 mEq/L in 52 (82.8%), 40–60 mEq/L in 7 (10%), and >60 mEq/L in 1 (1.6%). In the case with sweat test results >60 mmol/L, the sweat test result was found to be over 60 mmol/l again and the Delta F508 mutation was detected in the mutation analysis, and cystic fibrosis was diagnosed.

Children born because of in vitro fertilisation (IVF) are more likely to require neonatal intensive care because of the higher frequency of prematurity due to multiple pregnancies (39). It has been reported that respiratory distress syndrome develops more frequently, hospitalisation is longer, and perinatal death frequency increases in children born because of IVF compared with the control group. It has been shown that there is a statistically significant increase in the frequency of hospital admissions up to the age of 4 years, and this increase is particularly evident in the infant period (40). In addition, it has been thought that the drugs used for IVF (GnRH, purified FSH) may increase the frequency of allergic diseases and asthma in children born with IVF by affecting epigenetic modification and gene expression in the DNA structure of the fetus, but sufficient evidence has not been found (40). In our study, there was a history of IVF in 2 cases in the wheezing phenotype group. A case was born at 30 weeks of gestation weighing 1,300 grammes, and the other was born at 36 weeks of gestation weighing 2,900 grammes. Because IVF was not applied to a sufficient number of cases, no significant difference was found between the two groups.

Bronchopulmonary dysplasia (BPD) is a chronic lung disease in which oxygen dependence and/or the need for assisted ventilation continue in newborn babies due to reasons originating from the lungs. In a study conducted in China on the etiology of wheezy children, BPD was found to be 4.4% (41). In our study, this rate was determined as 0.5% (n=3). In Switzerland, preterm cases in the first year of their life with (n=78) and without (n=48) BPD were examined. Cough was detected in 80% of these cases, and wheezing was detected in 44%. Frequent contact with other children was evaluated as the major risk factor for wheezing (42). In our study, BPD was detected in 3 cases and they were under 1 year old. While cough and wheezing were present together in 2 cases, 1 case had only wheezing. In one case, the number of siblings

attending the nursery was 1, and in two cases, the number of siblings attending school was 2.

CONCLUSION

Wheezing is a common symptom in children. Although it is often caused by bronchiolitis, it can be difficult to distinguish it from infant asthma. Therefore, less common but not uncommon causes of wheezing, such as GERD, FBA, cystic fibrosis, and immune deficiency, should also be investigated. Early identification of the persistent atopic wheezing group, especially accompanied by atopy, is important in terms of controlling attacks before irreversible changes occur in the bronchi. Therefore, the first step of detailed examinations is the history and physical examination. To make this differential diagnosis and determine the treatment and prognosis, risk factors and etiology must be revealed. In this study, cases with specific diagnoses (such as bronchopulmonary dysplasia, GERD, and cystic fibrosis) and those with the wheezing phenotype group were examined in our cases between 1-24 months of age. It was found that the male gender was a significant risk factor in both groups, that the first attacks were significantly more frequent between 1 and 6 months in all cases, and that the attack season was significantly more in the winter months. While no significant difference was found in the history comparison, growth and developmental delay in the physical examination were found to be significantly higher in the specific diagnostic group. Among the sociodemographic characteristics, the presence of a smoker at home was found to be significantly higher for wheezing in the wheezing phenotype group. Higher total IgE levels were found in persistent atopic wheezing cases in the wheezing phenotype group compared with cases diagnosed with other wheezing phenotypes. In terms of serum eosinophil percentage, it was found to be significantly higher in cases diagnosed with persistent atopic wheezing and non-atopic wheezing compared with cases diagnosed with early transient wheezing. The results of this study suggest that we should be careful not to have a smoker at home to reduce the development of asthma or its severity in cases in the wheezing phenotype group and that diseases such as GERD, FBA, and cystic fibrosis, in addition to atopy and allergic asthma, may cause persistent wheezing in infants with wheezing.

Ethics Committee Approval: Since this was a retrospective study on patients treated in 2010 and 2012, ethics committee approval was not obtained.

Informed Consent: Since this was a retrospective study, consent was not obtained.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- A.F.Ç.; Data Acquisition- A.F.Ç.; Data Analysis/Interpretation- Ö.Ö.; Drafting Manuscript- A.F.Ç.; Critical Revision of Manuscript- Ö.Ö.; Final Approval and Accountability- A.F.Ç., Ö.Ö.

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REFERENCES

1. Arslan H. Hışıltılı çocuklarda demografik özellikler ve atakları etkileyen faktörler, Dokuz Eylül Üniversitesi Tıp Fakültesi, 201
2. Altıntaş DU. Hışıltılı Bebek. Çukurova Üniversitesi Tıp Fakültesi Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Allerji Bilim Dalı, Klinik Pediatri, 2002;1(2):73-78
3. Taussig LM, Wright AL, Holberg CJ, Halonen M, Wayne J, Morgan WJ, Martinez FD. Tucson Children‟s Respiratory Study: 1980 to present. J Allergy Clin Immunol 2003;111:661-75.
4. Phelean PD, Robertson CF, Olinsky AO. The Melbourne Asthma Study: 1964- 1999. J Allergy Clin Immunol 2002;109:189-94
5. Brand PLP, Baraldi E, Bisgaard H, Boner AL, Castro-Rodriguez JA, Custovic A et al. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. Eur Respir J 2008; 32: 1096-1110.
6. Tuncer A. Çocukluk çağında bronşiyal astma. Katkı Pediatri Dergisi: H.Ü.T.F 1997;18: 712-23.
7. Martinez FD. Asthma Phenotypes: Wheezy Infants and Wheezy Children. In Schwartz RH: Immunology and Allergy Clinics of North America. Philadelphia. WB Saunders. 1998, 25-34.
8. Morgan WJ, Stern DA, Sherrill DL, Guerra S, Holberg CJ, Guilbert TW et al. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. Am J Respir Crit Care Med. 2005; 172: 1253-8.
9. Berger I, Argaman Z, Schwartz SB, Segal E, Kiderman A, Branski D, et al. Efficacy of corticosteroids in acute bronchiolitis: short- and long-term follow-up. Pediatr Pulmonol 1998;26:162-6.
10. Hoeger PH, Niggemann B, Haeuser G. Age-related IgG subclass concentrations in asthma. Arch Dis Child 1994;70:179-82.
11. Go RO, Martin TR, Lester MR. A wheezy infant unresponsive to bronchodilators. Ann Allergy Asthma Immunol 1997; 78: 449456
12. Çevik D, Ecevit Ç, Altınöz S, Kocabaş Ö, Kavaklı T, Öztürk A. HıĢıltılı Çocuklarda Risk Faktörleri ve Etiyoloji. Toraks Dergisi. 2007;8:149-55.
13. Lewis S , Richards D, Bynner J, Butler N, Britton J. Prospective study of the risk factors for early and persistent wheezing in childhood. Eur Respir J 1995;8: 349-56.
14. Sherriff A, Peters TJ, Henderseon J, Strachan D; ALSPAC Study Team. Risk factor associations with wheezing patterns in children followed longitudinally from birth to 3(1/2) years. Int J Epidemiol 2001;30: 1473-84.
15. Ferguson DM, Crane J, Beasley R, Horwood LJ. Perinatal factors and atopic disease in childhood. Clin Exp Allergy 1997; 27: 1394-1401.
16. Rona RJ, Chinn S. Lung- function, respiratory illness and passive smoking in British primary-school children. Thorax 1993; 48: 21-25.
17. Young S, Le Souëf PN, Geelhoed GC, Stick SM, Turner KJ, Landau LI. Influence of family history of asthma and parental smoking on airway responsiveness in early infancy. N Engl J Med 1991;324:1168-73.
18. Y Chen , S Z Yu, W X Li. Artificial feeding and hospitalisation in the first 18 months, Paediatrics, 1988;81(1):58-62
19. Von Mutius E, Martinez FD, Fritzsch C, Nicolai T, Reitmeir P, Thiemann HH . Skin test reactivity and number of siblings. Br Med J 1994;308:692-4
20. Martinez FD, Wright AL, Holberg CJ, Morgan WJ, Taussig LM. Maternal age as a risk factor for lower respiratory illnesses in the 1st year of life. Am J Epidemiol 1992; 136:1258-68.

21. Henderson AJ , Sherriff A, Northstone K, Kukla L, Hruba D. Pre- and postnatal parental smoking and wheeze in infancy: cross cultural diff egences. Eur Respir J 2001; 18: 323-9.
22. Duff AL, Pomeranz ES, Gelber LE, Price GW, Farris H, Hayden FG , et al. Risk factors for acute wheezing in infants and children: viruses, passive smoke and IgE antibodies to inhalant allergen. Paediatrics 1993; 92:535-40.
23. Chang MY, Hogan AD, Rakes CP. Salivary cotinine levels in children presenting with wheezing to an emergency department. Pediatr Pulmonol 2000; 29: 257-63.
24. Chang MY, Hogan AD , Rakes GP, Ingram JM, Hoover GE , Platts-Mills TA,et al. Parental stress as a predictor of wheezing in infancy: a prospective birth-cohort study. Am J Respir Crit Care Med 2002; 165
25. Payne CB. Bronchiolitis, in Hilman B. Paediatric Respiratory Disease: Diagnosis and treatment. WB Saunders Company, Philadelphia 1993; 205-218.
26. Ownby DR, Johnson CC. Factors underlying the increasing incidence and prevalence of allergic diseases. In: Adkinson NF, Bochner BS, Busse WW (eds). Middleton's Allergy: Principles and Practise, 7th edition. China, Mosby Elsevier Publishers, 2009;769-79.
27. Strachan DP, Carey IA. Home environment and severe asthma in adolescence: a population based case–control study. BMJ 1995;311:1053-6.
28. Kerby GS, Larsen GL, Accurso FC, Deterding RR, Balasubramaniam V, Sagel SD. Respiratory tract and mediastinum. In: CarlW. White. Current Paediatric Diagnosis & Treatment (15th). USA McGraw-Hill Companies Inc, 2005:506- 508.
29. Hoeger PH, Niggemann B, Haeuser G. Age-related IgG subclass concentrations in asthma. Arch Dis Child 1994;70: 179-82.
30. Oner AF, Caksen H, Celik A, Cesur Y, Uner A, Arslan S. Serum immunoglobulins and immunoglobulin G subclasses with recurrent wheezing. Indian J Pediatr 2000; 67(12): 861-4.
31. Dodge J. Gastro-oesephageal reflux in infants. Acta Paediatr 1999; 88: 359-70.
32. Jain A, Patwari AK, Bajaj P, Kashyap R, Anand VK. Association of gastroesophageal reflux disease in children with persistent respiratory symptoms. J Trop Pediatr 2002; 48: 39-42.
33. Heffelfinger JD, Davis TE, Gebrian B, Bordeau R, Schwartz B, Dowell SF. Evaluation of children with recurrent pneumonia diagnosed by World Health Organisation criteria. Pediatr Infect Dis J 2002;21: 108-12.
34. Pereira KD, Mitchell RB, Eyen TP, Lazar RH. Tuberculous lymphadenopathy masquerading as a bronchial foreign body. Pediatr Emerg Care 1997;13: 329- 30.
35. Cengizlier R. Besin Alerjisi Olan Süt Çocuğuna Yaklaşım, Güncel Pediatri, 97; 61-63
36. Bayramgürler D, Apaydın R, Namlı S: Eozinofilik dermatozlar. T Klin Tıp Bilimleri 2002; 22: 602-611.
37. Mellis CM, Levison H. Bronchial reactivity in cystic fibrosis. Paediatrics 1978; 61: 446-450.
38. Çokuğraş H. Hışıltılı (Wheezy) Çocukta Etyoloji, Tanı, Ayırıcı Tanı ve Yardımcı Laboratuar Yöntemleri-Allerjiler Sempozyumu, 2001;61-71
39. Verstraelen H, Goetgeluk S, Derom C, Vansteelandt S, Derom R, Els G, et al. Preterm birth in twins after subfertility treatment: population based cohort study. BMJ. 2005; 331:1173
40. Klemetti Reija, Sevón Tiina, Gissler Mika, Elina H. Health of children born because of In Vitro Fertilisation Paediatrics 2006;118;1819- 1827
41. MM Yao, Wang KM, Xu QY, Wang GL, Liu XT. Aetiology and risk factors of infantile wheezing. Zhongguo Dang Dai Er Ke Za Zhi. 2011;13(3):195-8.
42. Pramana IA, Latzin P, Schlapbach LJ, Hafen G, Kuehni CE, Nelle M et al. Respiratory symptoms in preterm infants: burden of disease in the first year of life; Eur J Med Res. 2011; 16(5): 223–230.

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RESEARCH ARTICLE

Retrospective Examınatıon of Children with Beta Lactam-Drug Allergy: A Single-Center Experience

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ABSTRACT

Objective: The occurrence of drug reactions due to IgE or T-cell-mediated hypersensitivity reactions is referred to as drug allergy. Beta-lactam antibiotic (BLA) is the most common cause of drug allergy. In our study, we aimed to determine the true frequency of allergy in patients who presented to the children's immunology and allergy polyclinic on suspicion of BLA allergy and performed drug provocation test (DPT) and to evaluate the clinical, demographic, and laboratory characteristics of these patients.

Methods: Between 2017 and 2023, 141 patients (75 immediate reaction and 66 non immediate reaction) aged 0-18 years who applied to our hospital's pediatric immunology and allergy outpatient clinic with suspicion of BLA allergy and underwent DPT were included. Retrospective records from the last 6 years were examined from hospital data; age (month), sex, history of concomitant chronic diseases, history of additional allergic diseases, history of drug allergies in the family, type of reaction, serum total IgE, percentage of eosinophils (%), history of BLA use (penicillin V, penicillin G, ampicillin, amoxicillin etc.), specific IgE values, and drug intradermal test (IDT) results were recorded.

Results: In our study, 141 patients aged between 0 and 18 years were evaluated. 33 (23.4%) of them were IDT-positive. DPT was not performed because 24 patients did not have family permission and 9 patients experienced anaphylaxis. In our study, the BLA allergy rate determined by and/or skin tests was 26.9%, whereas the frequency of BLA allergy confirmed by DPT was 5.6%.

Conclusions: Beta lactam antibiotics are widely used worldwide and are the most common cause of drug-induced allergic reactions. Diagnosing a drug allergy thought to be associated with BLA based on history alone leads to the unnecessary use of broad-spectrum antibiotics and, consequently, to the development of antibiotic resistance. The patients should be referred to the child allergy department to be able to be definitively diagnosed for patients with suspected BLA drug allergy. Thus, we hope that unnecessary broad-spectrum antibiotics will be prescribed and that the use of expensive drugs will be prevented.

Keywords: Child, drug allergy, beta-lactam, penicillin, cephalosporin

INTRODUCTION

The occurrence of drug reactions mediated by hypersensitivity reactions via IgE or T cells is referred to as drug allergy (1). Beta-lactam antibiotics (BLA), which are widely used worldwide, are the most common cause of drug-induced allergic reactions (2). Maculopapular rashes and acute urticaria caused by viral infections in children are highly evaluated as allergic reactions to antibiotics used in the same period. Although allergic reactions to BLA drugs are reported in approximately 10% of the population, approximately 90% of patients can tolerate the drug after proper evaluation and diagnostic tests (3). For this reason, diagnosing a BLA allergy based solely on the story may lead patients to receive less effective, more broad-spectrum, or more expensive treatment (4).

The first step in diagnosing drug allergies in suspected cases is a detailed medical history (5). In accordance with the patient's condition, in vitro tests, intradermal tests (IDT), and the gold standard drug provocation test (DPT) should be performed (6).

This study aimed to determine the true frequency of BLA allergies in patients presenting with a pre-diagnosis of drug allergy at the Children's Allergy Clinic of Prof. Dr. Cemil Taşcıoğlu City Hospital and to retrospectively evaluate the clinical, demographic, and laboratory characteristics.

MATERIALS AND METHODS

Patient group

From January 2017 to January 2023, patients aged 0-18 years who were admitted to the Children's Allergy Clinic at Prof. Dr.

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Cemil Taşcıoğlu City Hospital, University of Health Sciences, with suspected allergies and who underwent diagnostic tests were included in the study. Patients' age (in months), gender, history of concomitant chronic diseases, history of additional allergic diseases, family history of drug allergies, type of admission reaction (immediate reactions: urticaria, anaphylaxis, angioedema, bronchospasm; non immediate reactions: maculopapular rash, fixed drug reaction, and others), BLA drug group (including penicillin V, penicillin G, ampicillin, amoxicillin, etc.), serum total IgE levels, eosinophil percentage (%), specific IgE values, IDT, DPT, and drug patch test results were recorded. Drug allergies other than BLA and those with missing data were not included in the study.

Patients were not asked for any additional examinations, nor was any questionnaire administered reactions occurring within the first hour after drug use classified as "immediate reactions," while those occurring after one hour were classified as 'non immediate reactions'(7).

Patients who experienced anaphylaxis following drug use were placed in the drug allergy group, and no diagnostic tests were performed for these patients.These patients were prescribed adrenaline auto-injectors and were given drug allergy tests for safe drug selection.

In vivo test

Specific IgE levels for penicillin V, penicillin G, amoxicillin, and ampicillin were assessed in all patients using the ImmunoCAP method, with values >0.35 kUA/L considered positive.

Skin tests

Patients suspected of having a drug allergy were tested with the suspected drug at least 4 weeks after the drug reaction, as recommended by the European Network for Drug Allergy (ENDA) (9,10). Initially, skin prick tests (SPT) were applied to the palmar side of the patient's forearm. In cases of negative SPT with the responsible drug, IDT was administered at diluted doses according to the test protocol of the predetermined drug. A positive test result was defined as swelling greater than 3 mm compared with the negative control 20 min after the test. The late reading of IDT was done 72-96 hours later.

Test drug patch

Patients with a history of late-type reactions, including penicillin G, penicillin V, ampicillin, amoxicillin trihydrate, potassium clavulate, cefixime, cefuroxime, and cefotaxime, underwent the drug patch test, and patients were evaluated after 48 and 96 hours.

Drug Provocation Test

All patients underwent DPT under hospital observation with the offending drug to confirm the diagnosis, except those with a history of drug-confirmed anaphylaxis or severe cutaneous reactions and those without family consent.

Each drug's recommended treatment dose was started at 1/100 or 1/10 and continued until the daily treatment dose was reached. When the treatment dose was reached or a positive reaction was observed, the test was terminated. Patients who could use the last dose of the drug without problems were kept under observation for at least 2 h. Patients without any symptoms were advised to use the drug at home for another 5 days in case of late reaction.

The test was considered negative when no reaction occurred.

Statistical analysis

The data encoded after the coding of the data" ifadesi fazladan bir tekrar içeriyor ve kafa karıştırıcı. Daha sade ve net bir ifade için: "The data obtained from the research were entered into SPSS (Statistical Package for Social Sciences) (Version 22 for Windows, SPSS Inc, Chicago, IL, USA) and analyzed. The suitability of all measured variables for normal distribution was assessed using the Kolmogorov-Smirnov Test. Continuous variables were expressed as medians (with minimum and maximum values) because they did not follow a normal distribution, whereas categorical data were expressed as numbers and percentages. The non-parametric test "Mann–Whitney U Test was used to compare continuous data across groups. Categorical data were compared using Pearson's chi-square test or Fisher's exact test. Univariate and multivariate binary logistic regression analyses were performed to identify risk factors for allergy type and drug provocation test results. Based on literature reviews of the variables included in the analysis, variables with a p-value < 0.20 were included in the statistical comparisons between groups.

It was considered appropriate to include variables with a p-value <0.20 in the statistical between-group comparisons conducted for the study, given the literature reviews of the variables to be modeled in this analysis. Highly correlated variables found in the multivariate analysis were included in the model. In all statistical comparisons, a significance level of $p < 0.05$ was considered.

RESULTS

The average age of the 141 patients included in the study was 127.6 ± 46.1 months, with a median age of 126 months (range: 12-254 months Of the patients, 77 (54.6%) were male and 64 (45.4%) were female. Age distribution analysis revealed that 35.5% of the patients were in the 73-120 months range, and 39.7% were in the 121-180 months range (Table 1). Among the patients, 45.5% had additional allergic diseases, and 12.8% had a family history of allergies.

İmmediate-type reactions were observed in 53.2% of patients, whereas non-immediate-type reactions were observed in 46.8%. IDT results were positive in 33 (23.4%) patients, whereas 8 (7.4%) of the 108 patients who underwent DPT tested positive. Table 2 presents the distribution of clinical and laboratory data of patients.

A single drug was responsible for allergic reactions in 120 patients (85.1%), whereas more than one drug was responsible in 21 (14.9%). In the evaluation, the drugs responsible for the allergy were penicillin in 127 (90.1%) patients, cephalosporin

Table 1. Demographic characteristics of the patients

Parameters		Total (n=141) n (%)*	Male (n=77) n(%)*	Female (n=64) n (%)*	p
Age (month)	Median (min-max)	126 (12-254)	120 (12-228)	131 (27-24)	0.23**
Age group (month)	12-72	16 (11.3)	9 (11.7)	7 (10.9)	0.60***
	73-120	50 (35.5)	30 (39.0)	20 (31.3)	
	121-180	56 (39.7)	30 (39.0)	26 (40.6)	
	≥181	19 (13.5)	8 (10.4)	11 (17.2)	

* Percentage of columns ** Mann–Whitney U test *** Pearson's ki-square test

Table 2. Clinical and laboratory data

Categorical Variables		n (%)*
Additional allergic disease	No	77 (54.6)
	Yes	64(45.4)
Family history of drug allergies	No	123 (87.2)
	Yes	18 (12.8)
Accompanying chronic disease	No	112 (79.4)
	Yes	29 (20.6)
The type of Reaction	Early	75 (53.2)
	Late	66 (46.8)
Reaction Form***	Urticaria	76 (46.1)
	Maculopapular rash	51 (36.2)
	Anaphylaxis	9 (6.4)
	Angioedema	5 (3.5)
	Bronchospasm	3 (2.1)
	Other ****	7 (5.0)
Drug skin test	Negative	108 (76.6)
	Positive	33(23.4)
Drug provocation test (n=108)	Negative	100 (92.6)
	Positive	8 (7.4)
Drug patch test (n=11)	Negative	9 (81.8)
	Positive	2 (18.2)
Responsible drug-specific IgE (n=114)	Negative	112 (98.2)
	Positive	2 (1.8)
Continuous Variables		Median (min-max)
Eosinophil (%)		2.4 (0-137)
Serum total IgE kU/L		83 (0.2-199.6)

** Percentage of column ** Additional allergic disease: Asthma, rhinitis, atopic dermatitis, atopic dermatitis, food allergy, chronic urticaria *** Some patients have more than one form of reaction **** Other: Serum Sickness-Like Condition*

in 35 (24.8%) patients, and penicillin + cephalosporin in 21 (14.9%) patients. Among the 127 patients with penicillin allergy, 17 (13.4%) were allergic to amoxicillin, 38 (29.9%) were allergic to ampicillin, and 72 (56.7%) were allergic to penicillin V. Among the 35 cephalosporin-allergic patients, 1st-generation cephalosporins were responsible for the allergy in 2 patients (5.7%), 2nd-generation cephalosporins in 14 patients (40.0%), and 3rd-generation cephalosporins in 22 patients (62.9%).

The age and median of patients with non-immediate reactions compared to the types of reactions were statistically smaller than the immediate type of the applicant (respectively p=0.001 and p= 0.002). According to the time of reaction, there were no significant differences between the groups in terms of additional allergic disease, family history of drug allergy, and presence of concomitant chronic diseases (p>0.05). The positivity of the DPT test was again higher in the non-immediate reaction group. However, there was no significant difference in the statistical level of the distributions between the groups (p=0.66). A comparison of some sociodemographic, clinical, and laboratory data according to the reaction time of the patients is shown in Table 3.

Table 3. Comparison of sociodemographic, clinical, and laboratory data according to response time

Parameters n (%)*		Early Reaction (n=75) n (%)*	Late Reaction (n=66) n (%)*	P[a]
Gender	Female	35 (46.7)	29 (43.9)	0.74
	Male	40 (53.3)	37 (56.1)	
Age group (month)	12-72	5 (6.7)	11 (16.7)	**0.002**
	73-120	19 (25.3)	31 (47.0)	
	121-180	38(50.7)	18 (27.3)	
	≥181	13 (17.3)	6 (9.1)	
Additional allergic disease	No	43 (57.3)	34 (51.5)	0.48
	Yes	32 (42.7)	32 (48.5)	
Family history of drug allergies	No	63 (84.0)	60 (90.9)	0.22
	Yes	12 (16.0)	6 (9.1)	
Accompanying chronic disease	No	60 (80.0)	52 (78.8)	0.85
	Yes	15 (20.0)	14 (21.2)	
Oral use of the medication	No	26 (34.7)	18 (27.3)	0.34
	Yes	49 (65.3)	48 (72.7)	
IM/IV drug use	No	43 (57.3)	46 (69.7)	0.12
	Yes	32 (42.7)	20 (30.3)	
Drug Skin Test	Negative	63 (84.0)	45 (68.2)	**0.027**
	Positive	12 (16.0)	21 (31.8)	
Drug provocation test (n=108)	Negative	58 (93.5)	42 (91.3)	0.66
	Positive	4 (6.5)	4 (8.7)	
Responsible drug-specific IgE (n=114)	Negative	56 (98.2)	56 (98.2)	1.00
	Positive	1 (1.8)	1 (1.8)	
Eosinophil (%), median (min-max)		2.45 (0.0-37.0)	2.1 (0.0-17.7)	0.95[c]
Total Ig E (IU/mL), median (min-max)		92.2 (0.2-155.2)	67.5 (0.8-199.6)	0.61[c]

* Sütun yüzdesi, [a]Pearson ki-kare test, [b] Fisher Exact test, [c]MannWhitney U test Other: Serum Sickness-Like Condition, IM: İntramuskuler, IV: İntravenöz

In the study, 108 (76.6%) patients underwent DPT, and 8 (7.4%) tested positive (Table 4). Among those who had a positive drug challenge test, 62.5% were male, 62.5% had additional allergic diseases, their ages ranged from 61 to 120 months, and their IDT results were negative. The frequency of oral drug use among patients with DPT was 75%. However, there were no statistically significant differences between the groups in terms of sociodemographic, clinical, and laboratory data (p > 0.05) (Table 5).

Table 4. Characteristics of patients with positive drug provocation test results

	Reaction type	Responsible Drug	IDT result	Reaction during drug provocation test
Case 1	Immediate	Penicillin+ Sefalosporin	Negative	Urticaria
Case 2	Immediate	Penicillin+ Sefalosporin	Negative	Urticaria
Case 3	Non-immediate	Penicillin+ Sefalosporin	Negative	Maculopapular rash
Case 4	Non-immediate	Penicillin	Negative	Maculopapular rash
Case 5	Non-immediate	Penicillin	Negative	Maculopapular rash
Case 6	Non-immediate	Penicillin	Negative	Maculopapular rash
Case 7	Immediate	Penicillin	Negative	Urticaria
Case 8	Immediate	Penicillin	Negative	Urticaria

Univariate binary logistic regression analyses performed to determine risk factors for DPT positivity, age, total serum IgE level, and the presence of additional allergic diseases were found to have no effect (p > 0.05). However, multiple drug use increased DPT positivity by 5.4-fold compared with single drug use (95% CI = 1.12-26.0; p = 0.036). Similarly, 3rd-generation cephalosporin use increased DPT positivity by 6.9-fold (95% CI = 1.38-34.2; p = 0.018). In the multivariate model, these factors did not have a combined effect on DPT positivity (p > 0.05 for all variables).

DISCUSSION

Beta-lactam antibiotics are widely used globally, and they are the most common cause of allergic reactions to medications (1). Maculopapular rashes and acute urticaria resulting from viral infections in children are often misinterpreted as allergic reactions to antibiotics administered during the same period. Relying solely on patient history for diagnosing BLA allergies can lead to unnecessary use of broad-spectrum antibiotics, which contributes to antibiotic resistance and economic costs (8).

After the diagnostic tests, more than 95% of the patients were safe to use this drug group (9). In the literature, the hypersensitivity rate due to BLA is reported to be between

Table 5. Comparison of sociodemographic, clinical, and laboratory data according to the results of the drug provocation test

Parameters		Drug Provocation Test (%)*		p[a]
		Negative (n=100)	Positive (n=8)	
Gender	Female	44 (44.0)	3 (37.5)	0.72
	Male	56 (56.0)	5 (62.5)	
Age group (month)	12-72	12 (12.0)	0 (0.0)	0.46 [b]
	73-120	38 (38.0)	2 (25.0)	
	121-180	38 (38.0)	4 (50.0)	
	≥181	12 (12.0)	2 (25.0)	
Additional allergic disease	No	58 (58.0)	2 (25.0)	0.13
	Yes	42 (42.0)	6 (75.0)	
Family history of drug allergies	No	87 (87.0)	7 (87.5)	1.00
	Yes	13 (13.0)	1 (12.5)	
Accompanying chronic disease	No	84 (84.0)	6 (75.0)	0.61
	Yes	16 (16.0)	2 (25.0)	
Oral use of the medication	No	28 (28.0)	2 (25.0)	1.00
	Yes	72 (72.0)	6 (75.0)	
IM/IV drug use	No	67 (67.0)	6 (75.0)	1.00
	Yes	33 (33.0)	2 (25.0)	
Reaction type	Urticaria	55 (55.0)	4 (50.0)	1.00
	Angioedema	4 (4.0)	0 (0.0)	1.00
	Maculopapular rash	37 (37.0)	3 (37.5)	1.00
	Other**	2 (2.0)	1 (12.5)	0.20
Intradermal test	Negative	98 (98.0)	8 (100.0)	1.00
	Positive	2 (2.0)	0 (0.0)	
Responsible drug-specific IgE (n=87)	Negative	80 (98.8)	6 (100.0)	1.00
	Positive	1 (1.2)	0 (0.0)	
		Median (min-max)		
Age (month)		121 (27-228)	13 (108-24)	0.10
Eosinophil (%)		2.6 (2.4-37.0)	1.2 (0.1-15.7)	0.34
Total Ig E (IU/mL)		115.0 (0.2-199.6)	14.3 (4.5-45.1)	0.17

* Percentage of column ** Other: Serum disease-like condition [a] Fisher Exact test , [b] Pearson ki-square test, [c] MannWhitney U test

6% and 16%, with a range of 1%–10% in children (10,11). In our study, 141 patients suspected of having BLA allergies underwent DPT, and only 5.6% tested positive. Among the IDT-positive patients who experienced anaphylaxis or who lacked family consent, 26.9% of them had a This result indicates that the actual frequency of drug allergies was lower, which is consistent with the findings of other studies. The risk factors

associated with drug allergies were also evaluated in our study. Multiple drug use increased the risk by 5.4 times compared with single drug use (95% CI = 1.12-26.0; p = 0.036), and 3rd-generation cephalosporin use increased the risk by 6.9 times (95% CI = 1.38-34.2; p = 0.018).

The risk factors associated with drug allergies were also evaluated in our study. Multiple drug use increased the risk by 5.4 times compared with single drug use (95% CI = 1.12-26.0; p = 0.036), and the use of 3rd-generation cephalosporins increased the risk by 6.9 times (95% CI = 1.38-34.2; p = 0.018).

Many patients who have been evaluated for suspected drug hypersensitivity may experience confusion because of multiple drug use at the same time. The frequency of allergy to more than one drug was assessed in a study by Orhan et al. (16), which reported a frequency of 2.4%. In a study conducted by Özhan et al. in Turkiye, 48.6% of patients with suspected drug allergy had a history of using multiple drugs simultaneously (17). A study by Dilber et al. conducted in our country found that 17.8% of patients had multiple drug allergies (18).

One factor that increased the risk in our study was the use of 3rd-generation cephalosporins, which are often administered intravenously (IV). It has been observed that the method of drug administration may also carry a potential risk for drug allergies. A study conducted by Akkelle found that drug allergies were higher in patients receiving parenterally administered drugs, although this difference was not statistically significant (19). In another study, 60% of the patients were given oral medication and 40% received parenteral medication because of DPT (8). In our study, 68.8% of patients used oral medications, whereas 36.9% used parenteral medications. Although more studies are needed to establish the exact risk of drug allergy, parenteral drug administration is believed to increase the risk.

Age is another risk factor for drug allergies, with children generally having a lower risk than adults. In our country, the average age is between 5.5 and 7.5 years (20, 14, 12). In other studies in the literature, the average age was 7–10 years (21-22). Although different results have been observed in various studies, it appears that the frequency of drug allergies increases with age. In our study, the average age of patients with BLA allergy was 80 months, and 52.5% of these patients presented at ages between 61 and 120 months; however, age was not identified as a risk factor in the regression analysis. It has been that the age-advancement hypothesis is supported by the occurrence of drug reactions if a patient is re-exposed to the same medication after being previously informed.

One known risk factor for drug allergy is a personal or family history of drug allergies, as demonstrated in numerous studies (21-24). In our study, 12.7% of participants had a family history of drug allergies, whereas only one of the eight patients with a positive DPT had a family history of drug allergies. This result may be attributed to the small number of patients. Zambonino et al. also reported that age, sex, history of drug allergies, or atopy were not identified as risk factors (25).

Drug reactions can range from mild to severe anaphylaxis and can affect multiple systems in the body (26). Physicians have reported that some children treated with BLA may experience urticaria and maculopapular rash (27). Of the 141 patients included in our study, 54% had urticaria, and 35% experienced maculopapular eruptions, consistent with the literature (17-28, 14).

Some laboratory parameters, such as elevated eosinophil counts and total IgE levels, are accepted as supporting findings for the diagnosis of drug allergies; however, this association has not been consistently demonstrated in recent years (23,29). In this study, eosinophil counts and total IgE levels were statistically compared between immediate and non-instantially reacting patient groups. The eosinophil and total IgE levels were higher in the immediate reaction group; however, there was no significant difference between the groups (p = 0.95 and p = 0.61).

There are also some limitations to our study. Data on suspected drug allergies were retrospectively collected from hospital records and parental reports. Although patients and parents can provide their medical history, they may not capture all the findings related to drug allergies.

In conclusion, beta-lactam antibiotics are widely used globally and are the most common cause of drug-induced allergic reactions (2). These reactions are often confused with rashes caused by viral infections in children, leading to unnecessary antibiotic use; therefore, diagnoses should be confirmed through diagnostic tests (3). As demonstrated in our study, the unnecessary use of multiple and parenteral medications should be avoided.

Ethics Committee Approval: This study was approved by the ethics committee of Prof. Dr. Cemil Taşçıoğlu City Hospital (23.01.2023 25).

Informed Consent: Written consent was obtained from the participants.

Peer Review: Externally peer-reviewed.

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REFERENCES

1. Simons FE, Ardusso LR, Bilò MB, El-Gamal YM, Ledford DK, Ring J et al. World Allergy Organization anaphylaxis guidelines: summary. *J Allergy Clin Immunol.* 2011;127(3):587-93.
2. Arga M, Topal E. Anaphylaxis in children: what is it? What is it not? *Clin Med Pediatr.* 2020;12(2):103-13.
3. Civelek E. Food allergy. *Turk J Pediatr.* 2020;14(3):199-199.
4. Borch JE, Andersen KE, Bindslev-Jensen C. Prevalence of suspected and challenge-verified penicillin allergy in a university hospital population. *Basic Clin Pharmacol Toxicol.* 2006;98(4):357-62.

5. Erkoçoğlu M, Mısırlıoğlu ED, Kocabaş CN. Diagnostic evaluation of drug allergy. *Turk J Pediatr.* 2015;9(1):66-70.
6. Brockow K, Garvey LH, Aberer W, Atanaskovic-Markovic M, Barbaud A, Bilo MB, et al. Skin test concentrations for systemically administered drugs: an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy.* 2013;68(6):702-12.
7. Dykewicz MS, Lam JK. Drug hypersensitivity reactions. *Med Clin North Am.* 2020;104:109-28.
8. Pichler WJ. Delayed drug hypersensitivity reactions. *Ann Intern Med.* 2003;139:683-93.
9. Ertuğrul A, Başkaya N, Esenboğa S, Özmen S. Suspected beta-lactam antibiotic hypersensitivity in children: experiences in a pediatric allergy clinic. *Guncel Pediatri.* 2021;19(1):1-8.
10. Sullivan JR, Shear NH. Drug hypersensitivity syndrome: what is the pathogenesis? *Arch Dermatol.* 2001;137(3):357-64.
11. Köse S, Tezcan D, Işik SA, Asilsoy S, Uzuner N, Anal Ö. Evaluation of children with suspected beta-lactam allergy: a retrospective study. *Turk J Pediatr.* 2017;11:40-5.
12. Tugcu GD, Cavkaytar O, Sekerel BE, Sackesen CA, Kalayci O, Tuncer A et al. Actual drug allergy during childhood: Five years of experience at a tertiary referral center. *Allergol Immunopathol.* 2015;43(6):571-8.
13. Sipahi Cimen S, Hizli Demirkale Z, Yucel E, Ozceker D, Suleyman A, Sayili U, Tamay Z, Guler N. Risk factors for challenge-proven beta-lactam allergy in children with immediate and non-immediate mild cutaneous reactions. *Int Arch Allergy Immunol.* 2023;184(6):539-49.
14. Aykan E. Retrospective examination of drug allergies encountered in children [Thesis]. Ankara: University of Health Sciences, Dr. Sami Ulus Women and Children's Health Education and Research Hospital; 2017.
15. Caubet JC, Kaiser L, Lemaître B, Fellay B, Gervaix A, Eigenmann PA. The role of penicillin in benign skin rashes in childhood: a prospective study based on drug rechallenge. *J Allergy Clin Immunol.* 2011;127(1):218-22.
16. Orhan F, Karakas T, Cakir M, Akkol N, Bahat E, Sonmez FM, et al. Parental-reported drug allergy in 6-to-9-year-old urban schoolchildren. *Pediatr Allergy Immunol.* 2008;19(1):82-5.
17. Özhan AK, Doğruel D, Altıntaş DU, Yılmaz M. Five-year experience of early-type drug reactions at Çukurova University Pediatric Allergy Clinic. *Ege Tıp Dergisi.* 2018;57(3):136-41.
18. Dilber, D.H., Ozceker, D., Terzi, O. Drug allergy in children: what is the actual frequency of drug allergies? *Sisli Etfal Hastan Tip Bul.* 2022;56(4):552-8.
19. Akkelle E. Retrospective evaluation of skin and drug provocation test results in patients with drug reactions [Thesis]. Edirne: Trakya University Faculty of Medicine, Department of Pediatrics; 2013.
20. Özmen S, Şahin M, Yöney A, Nilüfer AR, Arslan Z. Drug-related rashes in children: a single-center experience. *Turk Pediatri Arşivi.* 2011;46(1):3-7.
21. J. Le, T. Nguyen, A. V. Law, J. Hodding. Adverse drug reactions among children over a ten-year period. *Pediatrics.* 2006;118(2):555-62.
22. Temple ME, Robinson RF, Miller JC, Hayes JR, Nahata MC. Frequency and preventability of adverse drug reactions in pediatric patients. *Drug Safety.* 2004;27:819-29.
23. Lüleyap D. Retrospective evaluation of data from patients admitted for drug reactions [Thesis]. İzmir: Dokuz Eylul University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Allergy and Immunology; 2019.
24. Akkelle E. Retrospective evaluation of skin and drug provocation test results in patients with drug reactions [Thesis]. Edirne: Trakya University Faculty of Medicine, Department of Pediatrics; 2013.
25. Zambonino MA, Torres MJ, Muñoz C, Requena G, Mayorga C, Posadas T et al. Drug provocation tests for diagnosing hypersensitivity reactions to nonsteroidal anti-inflammatory drugs in children. *Pediatr Allergy Immunol.* 2013;24:151-9.
26. Orhan F, Civelek E, Şahiner ÜM, Arga M, Can D, Çalıkaner AZ, et al. Anaphylaxis: Turkish National Guideline 2018. *Asthma Allergy Immunol.* 2018;16.
27. Macy E, Schatz M, Lin CK, KY. The decreasing rate of positive penicillin skin tests from 1995 to 2007. *Perm J.* 2009;13(2):12.
28. Caubet JC, Kaiser L, Lemaître B, Fellay B, Gervaix A, Eigenmann PA. The role of penicillin in benign skin rashes in childhood: a prospective study based on drug rechallenge. *J Allergy Clin Immunol.* 2011;127(1):218-22.
29. Cavkaytar O. Evaluation of common-allergic drug reactions in childhood [Thesis]. Ankara: Hacettepe University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Immunology and Allergy; 2013.

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CASE REPORT

A Case of Acute Infantile Hemorrhagic Edema Confused with Child Abuse

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ABSTRACT

Acute infantile hemorrhagic edema (AIHE) is a type of leukocytoclastic vasculitis with a generally good prognosis and is observed in infants aged 4-24 months. It may be difficult to diagnose in some cases because its clinical findings are similar to those of many other diseases. Trauma and child abuse are among the differential diagnoses and should be first excluded. Although the exact cause of this disease is not known, it has been associated with infections, vaccines, and medications. Staphylococci, Streptococcus, and *Adenovirus* are the leading infective agents, while many other agents, such as *Escherichia coli* and Mycobacteria, have been suggested to be the cause of AIHE. Typically, purpuric skin lesions, edema, and fever are the presenting findings. Herein, we report the occurrence of the disease in a 6-month-old girl within a short period after vaccination.

Keywords: Acute hemorrhagic infantile edema, Finkelstein's disease, purpura

INTRODUCTION

Acute infantile hemorrhagic edoema (AIHE) is a rare but generally benign leukocytoclastic vasculitis. This disease is mostly observed in infants (between 4 and 24 months). Clinically, purpuric lesions on the skin, edoema, and fever are common findings. These lesions mostly occur on the cheeks, extremities, and auricles. Lesions usually heal spontaneously, leaving pigmentation. Although the etiology of it is not known, many cases have been reported after infections, vaccines, and some drugs being used (1-5).

Here, we present a case in which disease symptoms appeared within 6 hours of routinely administering combined vaccines [diphtheria-acellular pertussis-tetanus-inactivated polio-haemophilus influenza type b (DaBT-IPA-Hib)], oral polio (OPA), and hepatitis B (Hep-B)] to a 6-month-old girl.

CASE REPORT

A 6-month-old female patient was admitted to our emergency department with complaints of sudden edoema, redness, and bruising. Within a few hours, new ecchymotic lesions appeared, and they did not fade upon pressure application. First, it was swelling and then bruising; it appeared on the left arm, both sides of the left hand, the left leg, and both sides of the left and right feet, and was painless (**Picture 1a-c**). The family members stated that the patient was vaccinated with DaBT-IPA-Hib, Hep-B, and OPA early in the morning of the same day.

When the patient's medical history was questioned, it was learned that she was born at term and weighed 3,300 g vaginally. The patient was breastfed for the first 2 weeks after birth and then fed supplementary food. No history of medication use or infection before the lesions. No allergic reactions to foods, medications, or vaccines were observed. When the family history was asked, he had no history of similar or other diseases in either of his siblings.

There were no findings other than ecchymotic lesions on physical examination. At first admission, her fever was 37°C, and her pulse rate was 130 beats/min. Initial examinations in our emergency department revealed a white blood cell count of 21,770/mm3 (53.1% neutrophils, 41.8% lymphocytes, 4.2% monocytes, 0.8% eosinophils, and 0.1% basophils), hemoglobin of 8.6 g/dL, and a platelet count of 513,000/mm3. ALT: 12 U/L, AST: 33 U/L, CRP: 22.40 mg/L, INR: 1.13, Prothrombin time: 12.6 seconds. Venous blood gas and complete urinalysis were within normal limits.

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A superficial tissue ultrasound examination revealed mild edematous changes in the subcutaneous tissue in ecchymotic regions with linear fluid echogenicity. Transfontanel ultrasound and fundus examinations performed to exclude possible trauma to the child (child abuse) were normal. The patient, who was observed in our emergency department for a while and underwent relevant tests, was followed up and treated in our allergy and immunology department. The C3 level was: 1.32 g/L, C4 level: 0.30 g/L, ANA level: 1/100 (nuclear-granular) positive, ANCA level: negative, anti-ds DNA level: negative, Rheumatoid factor: 173 IU/L, D-dimer: 5,700 ugFEU/L, ASO: <57.50 IU/mL. We found that rhinovirus/enterovirus was positive in the respiratory system infection panel that we tested. The result of a 3-mm skin biopsy of the ecchymotic lesion on the patient's left arm was consistent with leukocytoclastic vasculitis. The patient we were following in our department was treated with 1 mg/kg/day methylprednisolone and 1 mg/kg/day pheniramine maleate for 5 days. The examination the next day revealed no fever or tenderness, and the lesions had begun to fade. The patient was discharged on the 6th day of hospitalization, and the ecchymotic lesions almost completely disappearing. (The patient gave her consent for this presentation.)

DISCUSSION

AIHE, also known as Finkelstein-Seidlmayer vasculitis or Seidlmayer purpura, was first described in 1913 by Snow in an article titled 'Purpura, urticaria, and angioneurotic edoema on the hands and feet'. According to the reported case series, most of the patients were men aged 2 years (1-4).

Although the exact cause of AHIE is not known, it is believed to be caused by vaccines, medications, and infections (5). The fact that our patient was positive for rhinovirus/enterovirus and the lesions appeared shortly after DaBT-IPA-Hib, Hep-B, and OPA vaccinations supports this view, but it leads to confusion about the real etiological trigger. Krause and his team proposed 4 criteria to help diagnose this disease (6). These criteria are as follows:

1) Purpuric rashes in children below 2 years old

2) Purpuric rashes accompanied by edoema on the face and extremities

3) No systemic or visceral lesions or skin lesions lasting several days to weeks

4) Lesions on the skin taking the shape of a target board within 24 to 48 hours and then regressing spontaneously within days or weeks.

Our patient findings typically met the criteria specified here. However, the ecchymotic lesions on the hands, feet, and forearms were more visible than those in other reported case examples (**Picture 1**).

Although edoema and lesions are frequently seen on the arms, legs, and ears in AIHE, trunk muscle involvement is very rare. Fever may usually accompany the lesions. In our case, edoema was evident on the extremities and ears, but fever was at normal levels at both presentation and during the follow-up period (7-11). In the treatment of our patient, antihistamine and methylprednisolone treatments mentioned in the literature were applied; the lesions regressed within a few days, and the patient's lesions completely resolved within 5 days (**Picture 2**).

The diagnosis is usually made by anamnesis and physical examination. There are no specific laboratory tests. Although sedimentation rate (ESR) and CRP levels are generally within the normal range in patients (12), CRP levels were increased in our patient. Mild lymphocytosis and eosinophilia-dominated leukocytosis can be seen in the hemogram; a slight increase in platelet levels can be seen (4,13,14). However, coagulation tests are generally normal (15). Urinalysis is often within the normal range, but microscopic hematuria and proteinuria have also been detected in some patients (12). Antinuclear antibody (ANA) and rheumatoid factor are generally negative, as in our patient (16). Patients with increased C3 and slightly decreased C4 levels have also been reported (2,17). The laboratory images mentioned were consistent with our patient's results.

When the biopsy material from the purpuric region is examined with a light microscope in these patients, karyorrhexis and purpuric-type vasculitic lesions that mostly involve the vessels of the upper and lower dermis can be seen. Fibrinoid necrosis can also be seen around and inside affected vessels, along with erythrocytes and leukocytes (2). We found that the biopsy results for our patient were consistent with the reported data.

The most frequently confused disease when diagnosing AIHE is Henoch-Schönlein purpura (HSP). Although ecchymosis and

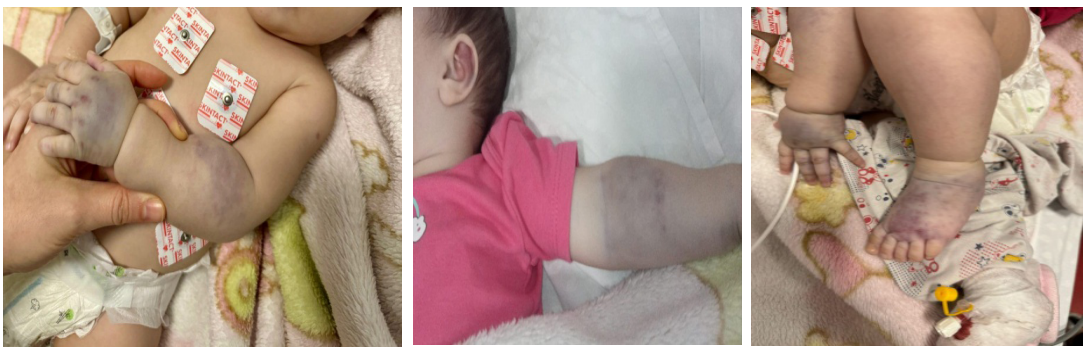

Figure 1a, b, c: Lesions indicative of trauma at initial presentation and at specific sites.

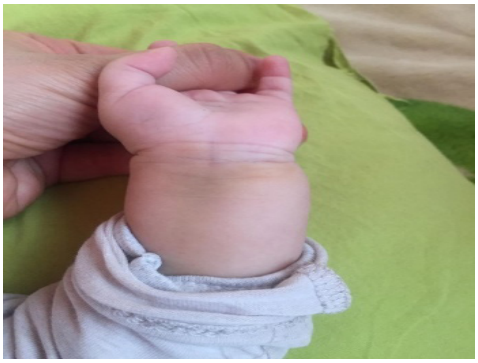
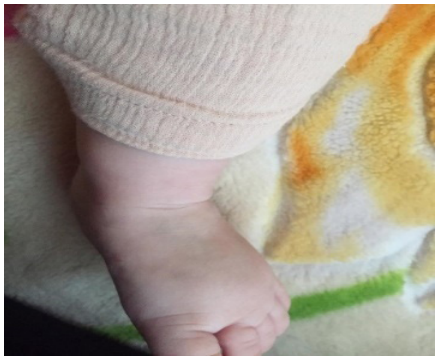

Figure 2a, b: Patient's lesions after discharge.

edoema are often seen together in AIHE lesions, HSP is more characterized by palpable ecchymotic (palpable purpura) lesions. While there is no visceral involvement in AIHE, involvement of other systems (gastrointestinal, kidney, etc.) is one of the findings of HSP. AIHE is usually seen in individuals aged 2 years, while HSP is more commonly seen in individuals between 3-10 years of age (1,17-19).

In differential diagnosis, it is necessary to distinguish AIHE from HSP, which is closely related to it; Kawasaki; Erythema multiforme; urticaria with hemorrhage (urticarial vasculitis); vasculitis caused by drugs; and conditions such as trauma and child abuse, which we would like to emphasize. For this purpose, as was done in our patient, fundus examination after a good anamnesis and trans-fontanel USG in individuals whose fontanels have not yet closed are the methods that can be used. Because purpuric rashes can occasionally occur after trauma, patients may recall trauma or child abuse. Purpuric rashes can be confused with AIHE, leukemia, and HSP rashes in children, especially by inexperienced physicians (20).

Child abuse is divided into 3 large groups: physical, sexual, and emotional abuse. Physical child abuse, which is related to our case, can be defined as the physical damage or injury to children under the age of 18 by their mother, father, or another person responsible for their care in a way that will harm their health. The possibility of physical abuse should be considered in every child presenting with an injury or signs of injury, such as purpuric rash. When this is suspected, a careful history should be taken, a physical examination should be performed, and routine radiological examinations and blood counts should be added to the examination (21).

In the evaluation made by taking the history, delay in bringing the child to the doctor, contradictory statements in the history, a history that does not match the physical results, recurrent and suspicious injuries, parents blaming the child or someone else for the injury, the child blaming the parents for the injury, a history of abuse in the parents, and the child appearing indifferent or overly anxious about the injury should suggest physical abuse. During physical examination, bruises in the calf/leg and genital area, soft tissue damage in different healing stages, special marks, such as hand/bite marks, numerous cigarette burns, liver or spleen rupture due to blunt abdominal trauma, cephalohematoma, subperiosteal hemorrhage, epiphyseal separation, metaphyseal fracture, radiological findings, such as periosteal calcification, retinal hemorrhage, eye damage, such as lens dislocation, multiple rib bone fractures, and ear damage with tympanic membrane rupture caused by traction, may be noted (22).

In some cases, upper respiratory tract symptoms, such as fever, cough, and dyspnea, were observed before lesions developed in patients with rhinovirus-based AIHE (23). Although upper respiratory tract infection was not identified in our patient, we believe that she may have been asymptomatic. In AIHE cases occurring after vaccination, lesions usually occur 2-3 weeks after vaccination (24–26). In our case, the fact that the lesions appeared very soon after vaccination and on the same day also distanced us from the etiology of vaccination. Once again, this is a case that perhaps shows that blaming vaccines as the cause of various diseases and disorders without being well-known and the reasons for vaccine hesitancy and rejection are not very accurate.

In conclusion, although AIHE can sometimes be confused with trauma, abuse, and hematological diseases in pediatric clinics, including emergency departments, it is a disease that can be easily diagnosed and has a benign course.

Informed Consent: Written consent was obtained from the participants.

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REFERENCES

1. Snow IM. Purpura, urticaria, and angioneurotic edema of the hands and feet in a nursing baby. JAMA 1913; 61:18–9.

2. Saraclar Y, Tinaztepe K, Adalioglu G, Tuncer A. Acute hemorrhagic edema of infancy (AHEI): a variant of Henoch-Schonlein purpura or a distinct clinical entity? J Allergy Clin Immunol. 1990; 86: 473-483.
3. Caksen H, Odabas D, Kosem M et al. Report of eight infants with acute infantile hemorrhagic edema and review of the literature. J Dermatol. 2002; 29:290-295.
4. Legrain V, Lejean S, Taieb A, Guillard JM, Battin J, Maleville J. Infantile acute hemorrhagic edema of the skin: study of ten cases. J Am Acad Dermatol. 1991; 24: 17-22.
5. Al Sufyani MA. Acute hemorrhagic edema of infancy: unusual scarring and review of the English language literature. Int J Dermatol. 2009; 48:617–22.
6. Krause I, Lazarov A, Rachmel A, Grunwald MM, Metzker A, Garty BZ, et al. Acute hemorrhagic edema of infancy, a benign variant of leucocytoclastic vasculitis. Acta Paediatr. 1996; 85:114–7.
7. Larreque M, Lesage B, Rossier A. Edema aguda hemorragico del lactante (EAHL) (purpura en escarapela) con edema postinfeccioso de Seidilmayer) vascularis alergica. Med Cutanea 1974; 11:165–174.
8. Ince E, Mumcu Y, Suskan E, Yalçınkaya F, Tümer N, Cin S. Infantile acute hemorrhagic edema: A variant of leukocytoclastic vasculitis. Pediatr Dermatol. 1995;12:224–227.
9. Lantner RR, Simon PR. Acute hemorrhagic edema of infancy. Pediatr Emerg Care 12: 111–112, 1996.
10. Saraçlar Y, Tınaztepe K. Infantile acute hemorrhage of the skin. J Am Acad Dermatol 24: 275–76, 1991.
11. Gonppryp, L.A., Todd, G. Acute hemorrhagic edema of childhood. Pediatr Dermatol. 1998;15:91–96.
12. Millard T, Harris A, MacDonald D. Acute infantile hemorrhagic edema. J Am Acad Dermatol 1999; 41: 837–39.
13. Karremann M, Jordan AJ, Bell N, Witsch M, Dürken M. Acute hemorrhagic edema of infancy: report of 4 cases and review of the current literature. Clin Pediatr (Phila). 2009;48(3):323-6.
14. N. Tomac, Y. Saraclar, I. Turktas, et al. Acute hemorrhagic edema of infancy: a case report. Clin Exp Dermatol. 1996;21:217–219
15. Cunningham, B. B., Caro, W. A., Eramo, L. R. Neonatal acute hemorrhagic edema of childhood: A case report and review of the English-language literature. Pediatr Dermatol. 1996;13:39–44.
16. Smitt JH, Vermeer MH, Faber WR. Acute hemorrhagic edema of infancy (AHEI). Clin Dermatol 2002; 20: 2–3.
17. Özdemir Ö, Avcı O, Akın İM, Büyükkayhan D. D-Dimer düzeyinin akut infantil hemorajik ödemde prognostik önemi. Güncel Pediatri. 2016;14(3):142- 6.
18. Sites LY, Woodmansee CS, Wilkin NK, Hanson JW, Skinner RB, Jr, Shimek CM. Acute hemorrhagic edema of infancy: case reports and a review of the literature. Cutis 2008;82:320–4.
19. Habif TP. Exanthems and drug eruptions. In: Habif, T. P. Clinical Dermatology: A Color Guide to Diagnosis and Therapy. 4th ed. Philadelphia, PA: Mosby; 2004:457-96.
20. Çoban M, Gündoğdu Çoban D, Pop S, Engin MMN, Özdemir Ö. Travma ile Karışabilen Bir Henoch- Schönlein Purpura Olgusu. Sakarya Med J 2023;13(2):329-33
21. Taner, Y., Gökler B. Çocuk istismarı ve ihmali: psikiyatrik yönleri. Hacettepe Tıp Dergisi 2004; 35:82-86.
22. Arthur HG. Physical abuse of children. In: Wiener JM, ed. Textbook of child adolescent psychiatry. 2nd ed. Washington: American Psychiatric Press, 1997; 687-98.
23. Al Murayshid AI. Acute Hemorrhagic Edema with extensive truck involvement and Rhinovirus infection association. Journal of Dermatology & Dermatologic Surgery. 2017; 21(1):27–30.
24. Saray Y, Seçkin D, Sarifakioğlu E, Güleç AT, Demirhan B. Acute infantile hemorrhagic edema: measles vaccination as possible triggering factor. Acta Derm Venereol. 2002;82(6):471-2.
25. Binamer Y. Acute hemorrhagic edema of infancy after MMR vaccine. Ann Saudi Med. 2015; 35(3):254-6.
26. Nacaroğlu HT, Saygaz S, Sandal ÖS, Karkıner CŞÜ, Yıldırım HT, Can D. Acute hemorrhagic edema of infancy after vaccination: A case report. J Pediatr Inf 2014; 8, 40-3.

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CASE REPORT

Rare Cause of Back Pain in a Paediatric Patient with Aneurysmal Bone Cyst: An Illustrative Case

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ABSTRACT

Spinal tumors are rare in the pediatric age. The most common symptoms of spinal tumors are neck, back, and waist pain. Diagnosis is often delayed in patients presenting with nonspecific symptoms (e.g. pain). Spinal tumors can cause mortality and significant morbidity due to bone damage, vascular involvement, and cord and nerve root compression. In this article, we present a 9-year-old male who complained of back pain for 3 months and was admitted to the emergency room with acute monoplegia which is diagnosed as an aneurysmal bone cyst at the level of the third thoracic vertebra. For patients who present with pain; a detailed history and careful neurological examination are important for diagnosis. Magnetic resonance imaging should not be delayed if there is any doubt. Aneurysmal bone cysts should be considered in the differential diagnosis.

Keywords: Child, back pain, bone cysts, spinal neoplasms

INTRODUCTION

Spinal tumours rarely seen in the paediatric population (1). A wide variety of findings depending on the biological characteristics of the tumour and its location, spread, and size can be observed. Neck, back, and waist pain are the most common symptoms for spinal tumours. Night pain, localised pain, and pain not induced by activity should be carefully examined for spinal tumours (2,3). Progressive motor loss, progressive scoliosis, gait disorders, and paraspinal muscle spasms are the most serious neurological symptoms. Spinal tumours are classified by their anatomical location; extradural tumours, intradural extramedullary tumours, and intramedullary tumours (1). Most commonly extradural tumours can be seen in the paediatric population. Diagnosis is often delayed due to nonspecific findings and its rarity. Significant morbidity due to bone damage, vascular involvement, and cord and nerve root compression can emerge (4). In this report, we present a paediatric patient who complained of back pain for 3 months and was finally admitted to the emergency department with acute monoplegia. The diagnosis was an extradural spinal tumour at T3 vertebra level. The patient operated in an emergency setting. The pathological examination was compatible with an aneurysmal bone cyst. Our aim in this study was to pay attention to spinal tumours that are very rare in childhood. Although it is rare; understanding the characteristic of spinal tumours and early diagnosis is necessary for proper management, improving outcomes and the chance of cure in children.

CASE REPORT

A previously healthy 9-year-old male was admitted to our emergency department with complaints of loss of sensation in his right leg and inability to move and walk, which started suddenly. No history of trauma or illness. He had mild back pain for 3 months; it did not affect his daily activities. There was no family history of neurological disease. Anthropometric measurements of weight and height were 50 kg (98 percentile due to World Health Organisation), 150 cm,, respectively. The patient's vital signs were in the normal range. On neurological examination, the cranial nerves were normal. Upper extremity bilateral muscle strength was 5/5, right leg muscle strength was 2/5 and left leg muscle strength was 4/5. He had hypoesthesia under the T4 dermatome. The lower extremity deep tendon reflexes were hyperactive bilaterally. The left

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Babinski reflex had a neutral response, and the right Babinski reflex was positive. The rest of the physical examination was unremarkable. Laboratory examination; completed blood counts, electrolyte, lactate dehydrogenase, uric acid, creatine phosphokinase, B12, folic acid, and coagulation parameters were within the normal range. Spinal magnetic resonance imaging sagittal non-fat-suppressed sequence T1-weighted precontrast (figure 1a) and postcontrast (figure 1b) revealed an expansile mass lesion at the T3 vertebral body that expanded in the corpus and protruded into the spinal canal and posterior elements. The mass extended into the neural foramen and caused a pathological fracture. The lesion showed similar signal characteristics to the muscle (figure 1a). Heterogeneous contrast enhancement was observed in the mass (figure 1b). Non-fat-suppressed sequence T2-weighted; the mass was heterogeneously hyperintense (figure 2). Fluid-fluid levelling was shown in the posterior part of the lesion (arrow). The peripheral blood smear and bone marrow aspiration evaluation were normal. Computed tomography of the thorax and abdomen taken for evaluating metastatic lesions revealed no pathology. The imaging showed that the vertebral mass primarily suggests bone-derived tumoral pathology. The patient was operated on in an emergency setting. The mass lesion involving the lamina, right pedicle, and partially corpus of the thoracic 3 vertebrae with significant paravertebral spreading was explored by T3 total and T2 partial laminectomy. A mostly extradural paravertebrally spread mass lesion was observed. The mass lesion excised grossly and totally. Because the right pedicle of the T3 vertebrae was excised and partial corpectomy was performed, thoracic posterior segmental transpedicular stabilisation was also performed. The pathological examination was compatible with an aneurysmal bone cyst. After the post-operative physical therapy and rehabilitation process, his lower extremity muscle strength was completely resolved at the end of the first year. There was no new tumoral lesion observed on spinal magnetic resonance imaging, and neurological examination was normal during the control examinations.

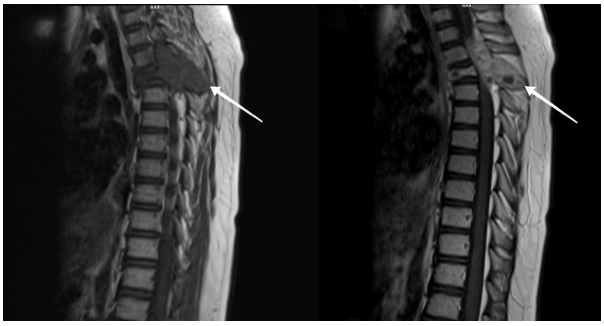

Figure 1: (a) Non-fat-suppressed precontrast T1W; (b) Non-fat-suppressed postcontrast T1W.

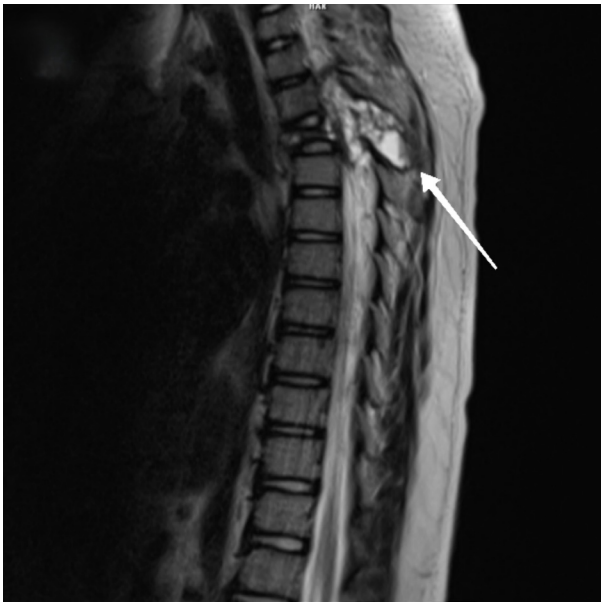

Figure 2: Non-fat-suppressed sequence T2W.

DISCUSSION

Extradural spinal tumours constitute approximately 30% of paediatric spinal tumours (5). Extradural spinal tumours may arise from the epidural space, vertebral bone and cartilage tissue, or paravertebral tissues (6). Extradural spinal tumours are mostly primary tumours arising from the bone elements of the spine (7). In our case, the tumoral lesion originated from the vertebral bone tissue.

Spinal tumour cases may present with a wide variety of clinical findings (4). Back pain is observed in 80% of children with spinal cord compression (8). Spinal tumours should be considered in cases of persistent pain that increases with movement (9). In healthy children without a history of trauma, back pain primarily suggests growing pains (10). Furthermore, paediatric back pain is common, but it is commonly associated with active and sedentary lifestyles, deconditioning, and excess body mass index. More than 80% of back pain in children is benign and mechanical in nature and resolves within 2 weeks with a natural course or conservative treatment (11).

The differential diagnosis for a paediatric patient presenting with back pain is extremely varied; muscle strains, stress, acute fractures, lumbar disc herniations, infections (especially tuberculosis in the epidemic region), rheumatologic causes (sacroilitis, ankylosing spondylitis), and although relatively rare; both bone-related malignant (Ewing sarcoma and osteosarcoma) or benign tumours (aneurysmal bone cyst, osteoid osteoma and osteoblastoma) and haematologic neoplasms (leukaemia and lymphoma) can occur in and around the spine in children (12). If back pain is not relieved with treatment, it should be examined carefully, including complex imaging, laboratory studies, and counselling as indicated (4). Our patient had back pain unrelated to blunt trauma for about 3 months. His family considered it as myalgia due to sedentary lifestyles, excess body mass index, or growing pains. They had never applied to a hospital for this complaint.

Spinal column pathology symptoms in paediatric patients vary depending on the location of the lesion (13). Cervical and thoracic spine tumour compression of neural tissue may cause upper motor neurone symptoms such as; paresis, hypertonia,

hyperreflexia, Babinski sign, sensory deficits, or myelopathy. Tumour compression or invasion in the lumbar and sacral region can be diagnosed with lower motor neurone symptoms such as; hypotonia, hyporeflexia, and bowel or bladder dysfunction. Young children and babies can present only with regression in motor skills, slow developmental progress, and agitation (14). Our patient had a sudden onset loss of muscle strength, sensation, and hyperreflexia on the lower extremity, and Babinski was positive.

The radiological gold standard evaluation method for spinal tumours is magnetic resonance imaging with or without contrast. It is important to imaging the entire spinal region with magnetic resonance imaging in the paediatric population (4,10). Computed tomography is useful in evaluating bone pathologies and identifying calcifications. However, in the paediatric population, whole spine imaging with computed tomography is contraindicated due to high radiation exposure (1). In our case, the tumoral lesion was diagnosed by whole spinal magnetic resonance imaging. After our patient was diagnosed with a spinal tumour, abdominal and thorax computed tomography was performed to investigate the metastatic lesions.

It is important to remove the spinal pressure by tumour excision in patients presenting with neurological deficits. The time between the onset of symptoms and surgical intervention is essential for neurological recovery. After surgical intervention, an improvement in neurological findings was observed in 50% of paediatric patients (8). The aim of surgery should be spinal and nerve root decompression and preservation of spinal stability. To avoid the recurrence of benign spinal tumour's important to remove the lesion completely during surgery (15). Our patient was operated on urgently by the department of neurosurgery. After the operation, the physical therapy and rehabilitation process was started. At the end of the first year, his neurological deficit was completely resolved.

Aneurysmal bone cyst is a benign, extradural blood-filled cystic bone neoplasm with a broad spectrum of skeletal involvement. The annual prevalence is 0.32 per 100,000 in the paediatric population and 0.14 per 100,000 in the general population. It is a rare neoplasm, accounting for approximately 2.5% of all bone tumours. It is most common in patients with incomplete skeletal development, especially in the first two decades. Although it can affect any bone in the body, craniofacial bones, vertebrates (especially the posterior elements), and the metaphyses of long tubular bones in the extremities are more commonly affected. Patients usually present with pain and swelling at the site of the lesion. Rarely, the first symptom is a pathological fracture; particularly in the extremity's major long tubular bones. Vertebral lesions mainly cause compression of the spinal cord or nerve roots. The diagnosis is made based on clinical, radiographic, and histological findings. Local recurrence occurs in up to 1/3 of the cases, especially within a few months after the first treatment, but recurrence after 2 years is very rare (16). Our patient's pathological examination was compatible with an aneurysmal bone cyst, and his age was in the first decade; like in the literature. Our patient presented with compression symptoms caused by a vertebral lesion; which is a bone frequently affected by aneurysmal bone cysts. No recurrence was observed in our patient during the 2-year follow-up.

CONCLUSION

Back pain without trauma may be due to spinal tumours in the paediatric age group. Detailed history and careful neurological examination are important in patients presenting with back pain. The early diagnosis of spinal tumours is essential for mortality and morbidity. Magnetic resonance imaging should not be delayed in cases of suspected spinal tumour lesions. Aneurysmal bone cysts should also be considered in the differential diagnosis of spinal tumours.

Informed Consent: Written consent was obtained from the participants.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- A.K.K., B.Z.Y.; Data Acquisition- A.K.K; Data Analysis/Interpretation- A.K.K., B.Z.Y., G.D.E., M.E.E.; Drafting Manuscript- A.K.K., B.Z.Y., A.O.K.; Critical Revision of Manuscript- A.O.K., M.E.F.; Final Approval and Accountability- A.K.K., A.O.K., B.Z.Y., G.D.E., M.F.E.

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REFERENCES

1. Ceyhan Bilgici M, Sarı Karabağ İ. Pediatrik Spinal Kitleler. Trd Sem.2019;7(3):406-425
2. Garg S, Dormans JP. Tumours and tumour-like conditions of the spine in children. J Am Acad Orthop Surg. 2005;13(6):372-381.
3. Pollono D, Tomarchia S, Drut R, Ibañez O, Ferreyra M, Cédola J. Spinal cord compression: a review of 70 paediatric patients. Pediatr Hematol Oncol. 2003;20(6):457-466.
4. Yıldız MZ, Çolak A, Erdi MF. Çocukluk Çağı Spinal Tümörler: Erişkin Olgulardan Farklılıklar. Türk Nöroşir Derg. 2023;33(1):50-58.
5. Wilson PE, Oleszek JL, Clayton GH. Paediatric spinal cord tumours and masses. J Spinal Cord Med. 2007;30(1):15-20.
6. Rossi A, Gandolfo C, Morana G, Tortori-Donati P. Tumours of the spine in children. Neuroimaging Clin N Am. 2007;17(1):17-35.
7. Alektoroff K, Papanagiotou P. Paediatric spinal tumours. Radiologie (Heidelb). 2023;63(8):609-613.
8. Tatarli N, Ceylan D, Ceylan N, Solmaz B, Barışık NÖ, Hiçdönmez T. Granulocytic Sarcoma Presenting With Acute Neurological Deficits: Case Report. Sakarya MJ. 2015;5(2):113-117.
9. Spacca B, Giordano F, Donati P, Genitori L. Spinal tumours in children: long-term retrospective evaluation of a series of 134 cases treated in a single unit of paediatric neurosurgery. Spine J. 2015;15(9):1949-1955.
10. Huisman TA. Paediatric tumours of the spine. Cancer Imaging. 2009;9 (Special issue A):45-48.
11. Murphy KP, Sanders C, Rabatin AE. Evaluation and Treatment of the Child with Acute Back Pain. Pediatr Clin North Am. 2023;70(3):545-574.

12. Rossi A, Gandolfo C, Morana G, Tortori-Donati P. Tumours of the spine in children. Neuroimaging Clin N Am. 2007;17(1):17-35.
13. Koshimizu H, Nakashima H, Ando K et al. Patient factors influencing a delay in diagnosis in paediatric spinal cord tumours. Nagoya J Med Sci. 2022;84(3):516-525.
14. Sundaresan N, Rosen G, Boriani S. Primary malignant tumours of the spine. Orthop Clin North Am. 2009;40:21-36.
15. Altunyuva, O., Eser Ocak, P., Doğan, Ş., Taşkapılıoğlu, M. Ö. Pediatrik Spinal Kitlelerin Retrospektif Analizi. Uludağ Üniversitesi Tıp Fakültesi Dergisi. 2023;49(3):291-296.
16. Nasri E, Reith JD. Aneurysmal bone cyst: a review. J Pathol Transl Med. 2023;57(2):81-87.