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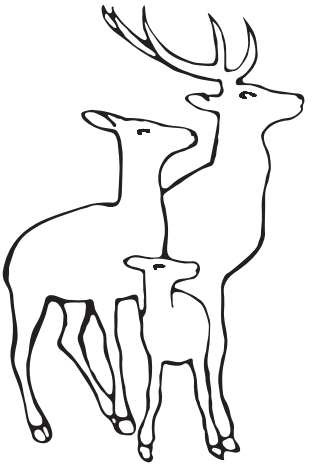

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The Turkish Journal of Pediatrics is a multidisciplinary, peer reviewed, open access journal that seeks to publish research to advance the field of Pediatrics. The Journal publishes original articles, case reports, review of the literature, short communications, clinicopathological exercises and letters to the editor in the field of pediatrics. Articles published in this journal are evaluated in an independent and unbiased, double blinded peer-reviewed fashion by an advisory committee.

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The Turkish Journal of Pediatrics: a year of transition for the Journal

We would like to announce that as of January 2023, the leadership of the Turkish Journal of Pediatrics has changed. Prof. Ali Düzova has become the new Editor-in-Chief, while Prof. Sinem Akgül resumes her role as Associate Editor. New to the editorial team are Prof. Eda Utine as joint Associate Editor and Assoc. Prof. Yılmaz Yıldız as Managing Editor. We are honored to assume the leadership of the official joint publication of the Turkish National Pediatric Society, Hacettepe University Institute of Child Health and The International Children's Center.

We would like to take this opportunity to thank the past editors Prof. Turgay Coşkun and Prof. Murat Yurdakök for their extraordinary contributions to the Journal over many years. Prof. Coşkun served as Editor-in-Chief for the last 30 years, from 1993 to 2022, and as Associate Editor from 1990 to 1993; Prof. Yurdakök served as Deputy Editor from 2016 to 2022, and as Associate Editor from 1989 to 2015 for the Journal. During their term, the Journal has been ranked in the Science Citation Index-Expanded (SCI-E) Journal List in 1998. Prof. Düzova and Prof. Akgül joined the Editorial Team in 2016 as Associate Editors, followed by other Section Editors. It has been a wonderful experience working with both Prof. Coşkun and Prof. Yurdakök. They will be greatly missed, and we are pleased that they will continue to be a source of encouragement and guidance that will ensure the Journal's continued success.

The leadership of our journal has transitioned smoothly as we have collaborated with an amazing team of section editors. The Journal has continued to flourish as we have focused on high-quality, timely reviewed studies and this has been reflected by the increase in our impact factor.

Our open access journal will continue to prioritize attracting submissions of high-quality science, providing a rigorous and timely review process, and publishing the best available science to inform efforts to improve the health and well-being of children worldwide. Additionally, we want to raise the Journal's profile among policymakers, professionals, and patient advocates. The Journal will also focus on structuring activities for young researchers and academicians to improve their abilities for writing and reviewing scientific manuscripts, designing and conducting studies. We anticipate the upcoming year and the publications our authors will send us.

Ali Düzova, *Editor-in-Chief*
Sinem Akgül, *Associate Editor*
Gülen Eda Utine, *Associate Editor*
Yılmaz Yıldız, *Managing Editor*

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Review

The evolution of the criteria for identifying the new concept of "Neonatal Near Miss": a systematic review

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ABSTRACT

Background. The concept of Near Miss, has been used in the field of obstetrics as a tool for assessing and improving the quality of care. However, there is no standardized definition or international criteria for identifying neonatal near misses. The current review aims to investigate the development of the neonatal near miss concept based on the results of studies conducted so far on neonatal near misses and their identification criteria.

Results. Sixty-two articles were retrieved by the electronic search, and after examination of different abstracts and reading of full texts, 17 articles were considered eligible meeting our inclusion criteria. All selected articles varied in terms of concept definition and criteria used. Neonatal Near Miss was defined as any newborn with pragmatic and/or management criteria who survived the first 27 days of life. All studies reviewed showed a Neonatal Near Miss rate that was 2.6 to 10 times higher than the neonatal mortality rate.

Conclusions. Neonatal Near Miss is a new concept that is currently being debated. There is a need for universal consensus on the definition and its identification criteria. Further efforts are needed to standardize the definition of this concept, including the development of criteria that can be assessed in a neonatal care setting. This is to improve the quality of neonatal care in every setting, regardless of the local level.

Key words: Neonatal Near Miss, neonatal morbidity, neonatal mortality, emergency neonatal care - identification criteria.

Maternal near miss (MNM) is a term used by the World Health Organization to describe a woman who nearly died but survived a complication during pregnancy, delivery, or 42 days after the end of pregnancy.[1] It also helps further investigate obstetric care by looking into complications that could have been prevented. At the same time, it has helped to recognize at-risk women, diagnose them, and start early and successful therapies. Additionally, it has made it possible to evaluate the standard of maternity healthcare.[1-3] Recent studies have shown the Near Miss tool in newborn care can improve the quality of care. It can also help detect healthcare errors and system deficiencies. This concept is similar to the widely accepted World Health Organization (WHO) tool, Maternal Near Miss (MNM). Although NNM is an evolving concept, there are no concrete systems or definitions for it. Currently, there are no standard way to identify and evaluate a NNM.[4]

According to some researchers, NNM refers to a morbid event that almost caused a neonate's death during the newborn period, such as diseases, interventions, and organ dysfunction, where the neonate only lived by luck or with high-quality care.[2,3,5] Other definitions, however, have focused on a shorter time frame of seven days.[6-8] Additionally, there is a

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dispute over the best illness severity indicators for NNM. Researchers in Brazil have utilized a variety of (pragmatic) standards to identify newborns as Near Misses, including low birth weight, gestational age at birth, and an Apgar score of 5 or below.[2,7,9] To the pragmatic criteria, some authors have added additional clinical management standards.[7-10] Researchers have since used clinical criteria, the existence of organ system dysfunction, and management criteria, using data from Morocco, Burkina Faso, Ghana, and South Africa, to classify newborns as Near Misses. These standards resemble the model that the WHO has suggested.[6,10,11]

NNM has received very little research so far, and there is a dearth of information on NNM cases, notably in Morocco and low- and middle-income nations. This review was conducted to examine the evolution of the NNM concept based on the findings of studies conducted thus far and to understand the similarities, differences, and gaps in these studies, which will provide avenues for future research. It was done in consideration of its usefulness as a tool for enhancing the quality of neonatal care.

Material and Methods

Research strategy

The research was conducted to investigate the NNM concept based on the results of the studies conducted so far and their identification criteria, according to the criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[12]

A systematic search of the literature was carried out, following the analysis of different articles and publications dealing with the subject without the restriction of time (until the end of 2021) the or language of origin. The electronic databases Medline, Embase, Scielo, PubMed, and Google scholar were searched based on keywords focused on the topic such as "near miss," "neonatal near miss," "neonatal mortality," "neonatal morbidity," "emergency neonatal care," "quality of care." The WHO and UNICEF websites were also consulted.

Inclusion and exclusion criteria

Sixty-two references were reviewed. Only studies with a clear definition of NNM, established criteria, and original data were considered eligible. In addition, we excluded studies and information published only as abstracts.

Data collection process

A data extraction table was used to identify data relevant to the study such as author's name, year, study title, objectives, study method, groups compared, sample, consideration of confounding and bias, the validity of tools, and conclusions supported by results.[13]

Results

To study the results of the research we reported the number of corresponding live births, the variables used as criteria for NNM, the specific neonatal data collection period, the neonatal mortality rate, and the NNM rate.

The findings of our analysis indicated that there is little literature on NNM. After looking through several abstracts and reading the entire contents of only 62 publications, 17 were deemed appropriate and matched our inclusion criteria (Fig. 1).

Between 2009 and 2021, 17 studies were released. Table I displays the evaluation of the selected studies' quality.

The concepts and selection criteria applied to each of the chosen articles vary. Table II compares the many studies that were compared in this evaluation.

Mukwevho et al.[14] from South Africa provided a useful clinical definition of severe acute newborn morbidity. This criterion was used in research by Avenant et al.[11] that used data from "Saving Babies: 2003-2005: Fifth South African Perinatal Care Survey" and included 3770 live births (LB). "The newborn's respiratory, cardiac, central nervous system, hypovolemia, hematologic, endocrine, renal, immunologic, musculoskeletal, and/or hepatic/

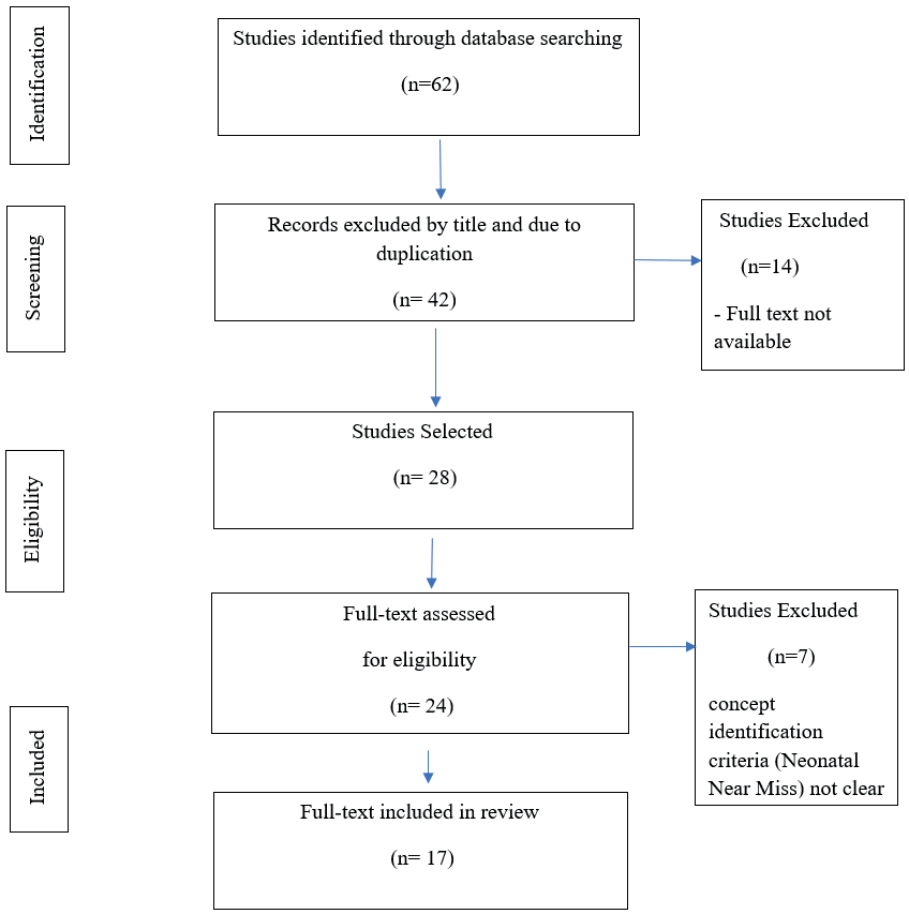

Fig. 1. Flow chart of process of systematic literature search in accordance with PRISMA.

gastrointestinal dysfunctions or failures were among the parameters evaluated".[11,14] The criteria were comparable to those that defined MNM. According to this study, the NNM rate was 24.7/1000 LB and the newborn death rate was 6.3/1000 LB.[11,14] A secondary analysis of the Brazilian dataset from the 2005 WHO survey on maternal and perinatal health was done as part of the Pileggi et al.[5] study. Of the 15169 LB included in this research, at least one of very low birth weight, gestational age at birth of under 30 weeks, and Apgar score < 7 at five minutes of life was present to identify NNM cases. The study's findings revealed an NNM rate of 21.4/1000 LB and an early neonatal mortality rate of 8.2/1000 LB.[5]

Pileggi-Castro et al.[7] have made other ground-breaking efforts to develop precise standards for identifying NNM instances by database analysis of two WHO investigations. The first was the Multi-country Maternal and Newborn Health Survey (WHOMCS) (2010-2011), which involved 359 health facilities in 29 countries. The second was the Global Maternal and Perinatal Health Survey (WHOGS (2004-2008)), which involved 373 health institutions in 24 countries. Two steps of analysis were carried out: Using WHOGS data first, pragmatic markers of severe newborn morbidity were created, and these markers were then verified using WHOMCS data. Too create a comprehensive set of criteria, the previously created pragmatic markers were merged with clinical management markers.[7,15]

Table I. Quality assessment of the studies included in the review.

Author/Reference	Relevance to this study	Aims clearly stated	Appropriate study method	Comparable study groups	Sample representative of target population	Confounding and bias considered	Validation of questions	Understandible tables / figures	Conclusions supported by results
Avenant. (2009)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pileggi et al. (2010)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	yes
Kale et al. (2017)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ronsmans et al. (2016)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Brasil et al. (2019)	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes
Wick (2017)	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes
Manandhar et al. (2014)	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes
Pileggi et al. (2014)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Silva et al. (2014)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Nakimuli et al. (2015)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bushtyreyvet al. (2016)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bakari et al. (2019)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Lima et al. (2018)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Mersha. (2019)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Ninama et al. (2019)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Suchma et al. (2021)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Table II. Comparison of the characteristics and results of the studies included in the review.

Author	Year	Site	Number of live births	Neonatal period (days)	Neonatal near miss rate	Neonatal mortality rate	Variables as criteria for neonatal near miss
Avenant (2009)	2009	South Africa	3770	Up to 28 days	24.7/1000 LB	6.3/1000 LB	Criteria of Mukwevo: Organ dysfunction/insufficiency similar to MNM
Pileggi et al (2010)	2010	Global survey (WHO)	15169	Up to 28 days	21.4/1000 LB	8.4/1000 LB	Birth weight < 1500 g Apgar < 7 at 5th min gestational age < 30 weeks
Kale et al (2017)	2011	Brazil	7315	Up to 28 days	123 (1.7%)	29 (0.4%)	Pragmatic markers: Birth weight < 1500 g Apgar < 7 at 5th min gestational age < 32 weeks
Ronsmans et al (2016)	2012	Benin, Morocco, Burkina- Faso	27857	Up to 7 days	427 cases	246 cases	Organ dysfunction/insufficiency similar to MNM
Brasil et al (2019)	2012	Brazil	24254	Up to 7 days	2098 cases	N/A	Birth weight < 1750 g Apgar < 7 at 5th min gestational age < 33 weeks
Wick (2017)	2012	Lebon	1178	Up to 7 days	17 cases	N/A	Birth weight < 1500 g Apgar < 7 at 5th min gestational age < 31 weeks
Manandhar et al (2014)	2013	Nepal Arghakhanchi	N/A	Up to 28 days	28 cases	N/A	Ventilation by mask Weight <1500g Infection Asphyxia at birth
Pileggi et al (2014)	2014	Country of WHOGS	277706	Up to 7 days	44.4/1000 LB	7.4/1000 LB	Birth weight < 1750 g Apgar < 7 at 5th min gestational age < 33 weeks
Pileggi et al (2014)	2014	Country of WHOMCS	309644	Up to 7 days	33.4/1000 LB 53.0/1000 LB 72.5/1000 LB	9.2/1000 LB 9.2/1000 LB 9.2/1000 LB	Pragmatic criteria Management criteria Combined the two criteria
Silva et al (2014)	2014	Brazilian national study	24061	Up to 28 days	39.2/1000 LB	11.1/1000 LB	Birth weight < 1500 g Apgar < 7 at 5th min gestational age <32 weeks Congenital malformation Mechanical ventilation
Nakimuli et al (2015)	2014	Uganda	2142	Up to 28 days	36.7/1000 LB	17.2/1000 LB	Modified criteria according to Pileggi and Avenant Birth weight < 1500 g Apgar < 7 at 5th min gestational age <30 weeks

CLAP: Latin American Center of Perinatology, GA: gestational age, LB: live births, MNM: maternal near miss, N/A: not available, NICU: neonatal intensive care unit, NNMAT: Neonatal Near Miss Assessment Tool, WHO: World Health Organization, WHOGS: WHO Global Maternal and Perinatal Health Survey, WHOMCS: WHO Multi-country Maternal and Newborn Health Survey

Table II. Continued

Author	Year	Site	Number of live births	Neonatal period (days)	Neonatal near miss rate	Neonatal mortality rate	Variables as criteria for neonatal near miss
Bushtyreyv et al (2016)	2015	Russia	16766	Up to 28 days	85.5/1000 LB	2.7/1000 LB	Pragmatic markers from Pileggi et al
Bakari et al (2019)	2015	Ghana multicenter study (NNMAT)	394	Up to 28 days	204 (74.5%) 233 (85.0%) 134 (48.9%) 16 (5.8%)	56 (82.4%) 60 (88.2%) 52 (76.5%) 7 (10.3%)	Birth weight < 1800 g Apgar < 7 at 5th min gestational age <33 weeks Management criteria, ventilation, cardiac massage, intubation Organ dysfunction Hematocrit > 30%. Hemoglobin <10dg/dl, bilirubin >10X GA Blood culture positive
Lima et al (2018)	2016	Brazil	1002	Up to 28 days	221 (22%)	44 (4.4%) early, 14 (1.4%) late neonatal deaths	Birth weight < 1750 g Apgar < 7 at 5th min gestational age <33 weeks And management criteria according to CLAP
Ninama et al (2019)	2016	India	2737 399 (NICU)	Up to 28 days	87.6/1000 LB	22/1000 LB	Pragmatic markers: Birth weight < 1500 g Apgar < 7 at 5th min gestational age <33 weeks
Suchma et al (2021)	2020	Biratnagar city of Morang, Nepal	1000	Up to 28 days	79/1000 LB	18/1000 LB	Birth weight < 1750 g Apgar < 7 at 5th min gestational age <33 weeks
Mersha (2019)	2019	Gamo and Gofa, Ethiopia	484	Up to 28 days	121 cases, 363 controls	N/A	Presence of at least one pragmatic marker or management criteria

CLAP: Latin American Center of Perinatology, GA: gestational age, LB: live births, MNM: maternal near miss, N/A: not available, NICU: neonatal intensive care unit, NNMAT: Neonatal Near Miss Assessment Tool, WHO: World Health Organization, WHOGS: WHO Global Maternal and Perinatal Health Survey, WHOMCS: WHO Multi-country Maternal and Newborn Health Survey

These analyses led to the following criteria being suggested.

Pragmatic criteria:
- Birth weight <1750 g
- Apgar score <7 at 5 minutes
- Gestational age <33 weeks

Management criteria: Use of:
- Parenteral antibiotics (up to 7 days and before 28 days of life)
- Nasal continuous positive airway pressure (CPAP)
- Any intubation within the first 7 days
- Phototherapy in the first 24 hours of life
- Cardiopulmonary resuscitation
- Vasoactive drugs
- Anticonvulsants
- Surfactants
- Blood products

The NNM rate for management markers was 53/1000 LB and for pragmatic, markers it was 37.4/1000 LB. With sensitivity and specificity of about 93% and a very strong odds ratio of 163, the combination of pragmatic and management criteria performed better.[7]

After accounting for any pragmatic or managerial variables, the early neonatal death rate was 9.2/1000 LB and the NNM rate was 72.5/1000 LB. The findings of this study demonstrated that NNM rates and early newborn mortality differed according to the NNM detection criteria employed.

Silva et al.[16] used "Birth in Brazil" data to conduct a study with 23940 LB. In this instance, 19 variables were employed to spot instances of NNM: Apgar score of seven at five minutes of life, gestational age between 32 and 37 weeks, birth weight between 1500 and 2500 g, and multiple deliveries are all risk factors. In terms of management, the following factors were noted: the requirement for mechanical ventilation, the need for additional oxygen following delivery, admission to neonatal intensive care, nasal CPAP, tracheal intubation in the delivery room, cardiac massage, resuscitative drugs, the requirement for phototherapy in the first 72 hours of life, the administration of surfactant, and the use of antibiotics in the first 48 hours of life.

In contrast, Ronsmans et al.[6] studied NNM cases in low- and middle-income countries by analyzing at the incidence of NNM cases and deaths in 17 hospitals in Benin, Burkina Faso, and Morocco (2012-2013). These researchers used clinical characteristics, such as the existence of organ system dysfunction, and management criteria to classify newborns as NNM, which is similar to how the WHO defines MNM.[6] The study's results showed that stillbirths and NNM cases varied from 23 to 129 per 1000 LB in Moroccan and Beninese hospitals, respectively, and that perinatal mortality (from 17 to 89 per 1000 LB) were more frequent than NNM (from 6 to 43 per 1000 LB).

Between October 2010 and April 2013, Manandhar et al.[17] conducted a prospective study on NNM cases in Nepal at various healthcare facilities. The only criteria utilized in this analysis to identify NNM cases were mask ventilation, extremely low birth weight (birth weight 1.5 kg), and potentially severe bacterial infection (PSBI). There have been 28 cases of NNM reported in various hospitals. The rate of NNM in the same country, as determined by Suchma's research, was 79/1000 LB.[18] Using management and pragmatic criteria, NNM cases were identified. The pragmatic criterion with the highest frequency was birth weight <1750 g (20/65; 30.7%), followed by the Apgar score <7 at five minutes after birth (41/65; 63.1%). Only one newborn met the three pragmatic criteria.

In India, Ninama et al.[19] discovered results that were essentially identical. During the study period, there was a newborn death rate of 22 per 1000 LB while the NNM rate was 87.6 per 1000 LB. The neonatal intensive care unit (NICU) level was used for this study. In this study, NNM was defined as neonates admitted to the NICU who met any of the following criteria: birth weight less than 1500g, gestational age less than 30 weeks, and Apgar score less than 7 at 5 minutes.

A prospective cohort study was conducted by Nakimuli et al.[20] in two referral hospitals in Uganda. Clinical management criteria, the presence of organ system dysfunction, and the provision of newborn care were used to identify NNM cases. The authors used the two managerial and pragmatic criteria developed by Pileggi-Castro et al.[7] but modified the criteria for gestational age and birth weight to be less than 30 weeks and less than 1500 g, respectively.

According to a study by Bushtyrev et al.[21] in Russia, which examined NNM cases in the city of Rostovondon between January 2011 and January 2015 using just the pragmatic markers created by Pileggi-Castro et al.[7], the incidence of NNM was 85.5% per 1000 LB out of 16588 LB.

In six public maternity hospitals in the Brazilian states of So Paulo and Rio de Janeiro, Kale et al.[22] conducted cohort research in 2011. The definitional parameters used to identify NNM occurrences were birth weight less than 1500 g, gestational age less than 32 weeks, and an Apgar score of five minutes less than seven. Out of the 7126 LB that were selected, 123 occurrences of NNM and 29 neonatal deaths were documented.

According to the following criteria (Apgar 7 at 5 minutes, weight 1750 g, or gestational age 33 weeks), NNM cases were found in a cross-sectional study carried out in Brazil by Brasil et al.[8] NNM cases survived for at least 7 days after birth. Out of 24,254 NV, 2,098 cases of NNM were found, with an incidence of (89.9%) concentrated in the public sector. However, when birth weight and gestational age were combined, both the public (43.5%) and private (46%) sectors reported nearly comparable incidences of NNM.

Lima et al.[9] used the new concept of NNM developed by the Latin American Center of Perinatology (CLAP) (pragmatic and/or managerial criteria or combination of both criteria) to conduct a prospective cohort analytical investigation in northeastern Brazil. A total of 1002 LB were present, 221 (22%) of which were NNM cases, 44 (4.4%) of which were early neonatal deaths, and 14 (1.4%) were late neonatal deaths. NNM prevalence was 220/1000 LB. A prospective, observational, multi-site investigation was carried out by Bakari et al.[10] in two tertiary referral hospitals in southern Ghana. To identify NNM cases, the study team developed the Neonatal Near Miss Assessment Tool (NNMAT), a tool with four categories: organ dysfunction, interventions made, evidence of severe consequences (matching pragmatic criteria), and investigations made (first 7 days of life). 394 newborns in all were enrolled, successfully screened with NNMAT, and followed up until age 28 at both sites. The findings of this investigation revealed various NNMAT categories, including:

-NNMAT category 1: (Apgar <7 at 5 minutes, weight <1800g, gestational age at birth <33 weeks, T°<35° or >39°, jaundice) 204 (74.5%) NNM and 56 (82.4%) neonatal death.

-NNMAT category 2: (management criteria) 233(85.0%) NNM and 60(88.2%) neonatal death.

-NNMAT category 3: (Respiratory, gastroenterological, and neurological organ dysfunction) 134 (48.9%) NNM and 52 (76.5%) neonatal death.

-NNMAT category 4: (Hematocrit >30%, hemoglobin <10g/dl, serum bilirubin >10X gestational age and positive blood culture) 16 (5.8%) NNM and 7 (10.3%) neonatal death.

Between 2019 and 2021, multiple studies in Ethiopia[23-30] were carried out at the level of the various regions of the country. using the new concept of Neonatal Near misses formulated by CLAP. NNM instances were almost ten times more frequent than neonatal mortality, accounting for 23.3 to 33.4% of the cases analyzed. In contrast, a standard structured approach was employed in the two investigations in Southern Ethiopia from Mersha et al.[30] in 2019 and Wondimu et al.[27] in 2020 to identify NNM events based on the presence of at least one pragmatic or management marker.

Wick[31] did a study on MNM and NNM cases in four public hospitals in the Middle East in Lebanon. Any newborn with extreme morbidity (weight less than 1.5 kg, gestational age at birth less than 31 weeks, and Apgar less than or equal to five minutes) who survived the condition within the first seven days of life was referred to as an NNM. Four cases of MNM and seventeen cases of NNM were found out of a total of 1178 newborns. Santos et al.[15] presented a comprehensive study in 2015 that suggested combining the three pragmatic criteria with the clinical management criteria for identifying NNM cases. Four studies, which were also covered above, served as the foundation for these recommendations.[5,7,11] It was also emphasized how important it is to standardize both the NNM concept and the standards used to evaluate its applicability at various levels.

In the same sense, a narrative study conducted in India by Surve et al.[32] showed the rate of NNM varies from 21 to 72% in the different studies analyzed, due to the divergence of criteria used. This study recommended the inclusion of additional management criteria, and congenital malformations.

Santos et al.[15] presented a comprehensive study in 2015 that suggested combining the three pragmatic criteria with the clinical management criteria for identifying NNM cases. Four studies, which were also covered above, served as the foundation for these recommendations.[5,7,11] It was also emphasized how important it is to standardize both the NNM concept and the standards used to evaluate its applicability at various levels.

A table with information from the 17 studies that were examined was put up to compare the evaluated factors with the related indicators of newborn mortality rate, NNM rate, and (Table II). Studies that employed longer neonatal periods (up to 28 days) and research that mixed pragmatic and management criteria generally had greater rates of newborn near misses, whereas studies that used more thorough criteria for detecting neonatal near misses had lower neonatal mortality indices.

Discussion

The definition of the NNM concept still poses a problem regarding the elements to be taken into consideration, there are no common recognition criteria at the international level. Indeed, most of the studies carried out so far have been based on the fundamental work of Pileggi et al.[5,7] NNM has been defined as newborns who suffer a life-threatening complication after birth and survive the first 28 days of life.[2,5,9,11,16,18-21,27,30] However, other definitions have used a shorter period of 7 days.[6-8,31] There is also disagreement on the most appropriate markers of complication severity that identify and evaluate NNM cases.

To determine if a newborn was a case of NNM, the researchers evaluated a number of characteristics. These requirements include "pragmatic markers" with discrepancies, like low birth weight (1500 g or 1750 g), low gestational age at birth (30, 31, 32, or 33 weeks), and an Apgar score of less than 5 or 7.[2,5,7,8,19-21,31] They are viewed as pragmatic since crucial information is widely accessible in medical literature and healthcare databases, and because the classification is simple to utilize for clinical and epidemiological purposes.[15] In addition to data accessibility, some studies have employed the criteria of preterm and perinatal asphyxia, the two main causes of neonatal death, to aid in the development of a practical definition of NNM. a pragmatic set of criteria that can be used in various socioeconomic circumstances and in the absence of applied care technologies to more accurately identify newborns with severe neonatal morbidity.

In a similar vein, CLAP recommends classifying newborns as NNM if they meet pragmatic and/or management criteria and have made it through the first 27 days of life. Even while each study's selection of criteria, like preterm and hypoxia, was identical, how these indicators were applied varied from study to study.

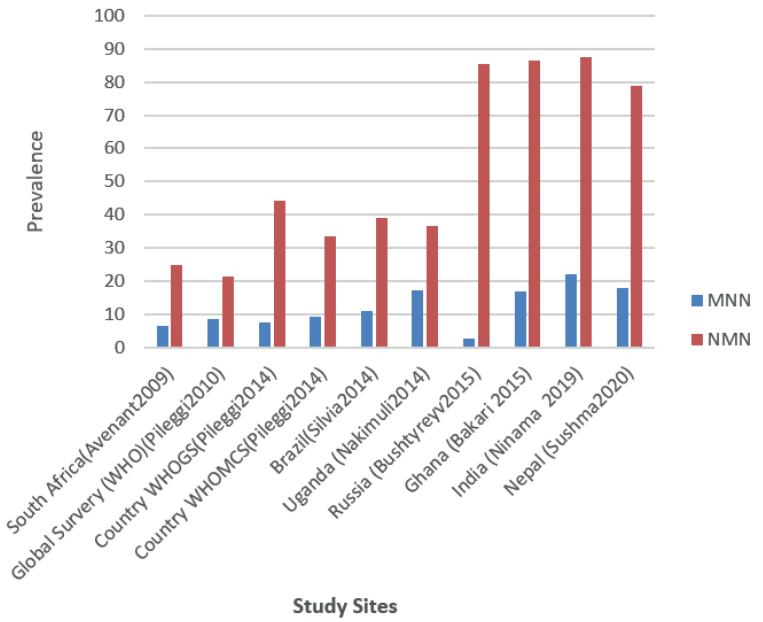

Fig. 2. Multi-country maternal and newborn health survey.

Indeed, some have used only pragmatic markers, others have combined them with management markers and few studies have proposed their own criteria for the classification of NNM cases.[10,17] Notwithstanding, we find that the combination of both pragmatic and managerial markers has generated a higher number of NNM cases.

While other researchers have used management criteria to develop the NNM concept, some investigators have expanded the pragmatic criterion to include mechanical ventilation and congenital malformations.[16,17] The latter criteria, which indicate the presence of the finest healthcare circumstances, maybe more significant for nations with low death rates and perform better than the pragmatic markers.[7,9,27,31] In contrast, research using information from Morocco, Burkina Faso, and Uganda classified a newborn as a case of NNM using clinical characteristics, organ system dysfunction, and management criteria is similar to how the WHO defines a case of NNM.[6,10,11]

The rate of NNM was found to be 2.6 to 10 times greater than the newborn death rate in all the studies that were examined (Fig. 2). Unfortunately, due to the significant differences in how the notion of NNM is operationalized, direct comparisons of NNM rates across studies were not feasible. This result supports the findings of Wondimu et al.[27] who argue that the various research adoption of different criteria caused the NNM magnitude to vary significantly. The majority of research is also retrospective, and some studies have only analyzed NNM instances in certain contexts, such as referral health facilities or tertiary levels, and under certain circumstances, such as obstetric complications, as predictors of NNM.[26-30]

In addition to pragmatic and/or management criteria for defining NNM, seven studies have described the association between maternal complications and the occurrence of NNM cases.[9,18-21,27,30]

After reviewing the literature, it seems useful to choose criteria for defining the NNM concept that is simple, practical, and easy to use in all healthcare institutions. Clinicians, managers, and other healthcare specialists should all be able to use these factors to make decisions. Regardless of the level of local infrastructure,

they must be stable in terms of severity and suitable to a range of contexts. It is recommended that, among the results now available, the pragmatic NNM criteria be applied whenever practical.

It is recommended to employ the three criteria (Apgar 7, birth weight 1750 g, and gestational age 33 weeks) that were found and covered by the largest WHO study for this purpose. All three criteria are among the crucial health indicators that are regularly gathered and can be calculated after the fact. In nations with higher resources, the combination of the three criteria plus the management criteria appears to be the optimum method for identifying NNM cases for a more thorough prospective examination.[11]

Investigating NNM, which shares many characteristics with neonatal mortality in developed nations like Australia where neonatal mortality is very low, will not only increase the number of cases that can be evaluated but is also of interest to providers because it may be less dangerous to them as it deals with survivors.[33] Given the similarities between NNM and neonatal deaths, applying the NNM concept appears to be a potential strategy for raising the standard of healthcare by exposing service gaps and offering a crucial chance to improve care delivery.

Our study contributes a pertinent contribution by focusing on the definition of NNM in light of various criteria and markers employed by various studies completed thus far, given that the concept is still new and up for debate.

The definition and standards for defining NNM appear to require universal agreement. No matter the local level, having straightforward, relevant criteria can raise the standard of newborn care everywhere.

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Ethical approval

The study protocol was approved by the Ethics Board of the Faculty of Medicine and Pharmacy, Mohammed University in Rabat, Morocco (Ethical Approval No: C64/20) delivered on February 24th, 2021.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: CK, BA, BF; data collection: CK, AF; analysis and interpretation of results: CK, LFZ, BF; draft manuscript preparation: CK, BA, AF, BF, LFZ.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Attitudes of parents with children aged 12-18 to COVID-19 vaccines for themselves and their children

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ABSTRACT

Background. The incidence of vaccine hesitancy is increasing in many countries. This study aims to determine parents' attitudes and related factors regarding COVID-19 vaccine acceptance for themselves and their children aged 12-18.

Methods. A cross-sectional survey was conducted on parents between 16th November and 31st December 2021, after COVID-19 vaccines were initiated for children in Türkiye. In the survey, the sociodemographic characteristics of the parents, whether they and their children were vaccinated against COVID-19, and if not, the reasons for this were asked. Multivariate binary logistic regression analysis was used to evaluate the factors affecting parents' refusal to vaccinate their children for COVID-19.

Results. Three hundred and ninety-six mothers and fathers were included in the final analysis. Overall, 41.7% of parents reported vaccine refusal for their children. COVID-19 vaccine refusal was higher in mothers younger than 35 ($\beta = 6.5$, $p = 0.002$, 95% CI: 2.0-23.1), children aged 15 and younger ($\beta = 2.3$, $p = 0.001$, 95% CI: 1.4-3.7). Concerns about the side effects of the COVID-19 vaccine (29.7%) and their children not wanting to be vaccinated (29.0%) were the most common causes of COVID-19 vaccine refusal.

Conclusions. In the present study, the rate of children not vaccinated due to COVID-19 vaccine refusal was relatively high. Parents' concerns about vaccine side effects, as well as their children's unwillingness to be vaccinated, suggest that both parents and adolescents should be informed about the importance of COVID-19 vaccines.

Key words: COVID-19, vaccine acceptance, parent, children.

In the three years since the onset of the coronavirus disease 2019 (COVID-19) pandemic, more than 600 million confirmed cases of COVID-19, including more than 6 million deaths, have been reported worldwide.[1]

According to the COVID-19 data reported worldwide, Türkiye is one of the most affected countries, with more than 17 million cases and 100,000 deaths reported as of January 2023.[1,2] The most important approach to controlling the pandemic is to provide immunization against the COVID-19, so vaccine studies have been prioritized. Like many countries, COVID-19 vaccine studies and vaccine applications continue with great effort in Türkiye.

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The first vaccination process in Türkiye started with the inactive COVID-19 vaccine (CoronaVac®) on 13th January 2021. Then, as of 2nd April 2021, the mRNA COVID-19 (Pfizer-BioNTech®) vaccine was started for adults. According to the data of the Ministry of Health of the Republic of Türkiye, the rate of individuals aged 18 and over who have received at least two doses of the COVID-19 vaccine was 85.6%.[2]

The COVID-19 vaccine for individuals under 18 years was first administered on 18th August 2021, over 15 years of age to healthy children and 12-15 years with chronic disease. As of 5th September 2021, all children aged 12 and over started to be vaccinated against COVID-19 before face-to-face education in schools.[2] There is no data yet on the rate of COVID-19 vaccination amoung children in our country.

Vaccine hesitancy is defined as a delay in accepting or rejecting a vaccine despite the availability of vaccination services.[3] The incidence of vaccine hesitancy is increasing in many countries, leading to the World Health Organization recognizing vaccine hesitancy as a significant threat to global health in 2019.[4] Recently, fears about vaccine safety and long-term side effects stemming from the novelty of the COVID-19 vaccine have revealed COVID-19 vaccine hesitancy.[5] It is stated that the vaccine should cover 55% to 82% of the population to provide herd immunity against Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2); however, COVID-19 vaccine hesitancy threatens the achievement of herd immunity.[6,7] Since children make up 27.2% of Türkiye's population, the vaccination rate of children is significant for increasing community protection against COVID-19.[8] Since parents play a leading role in the acceptance of the COVID-19 vaccine for their children, we aimed to determine parents' attitudes regarding the administration of COVID-19 vaccines to their children of vaccination age and themselves, the relationship between their vaccination status and vaccination of their children, the frequency and reasons of hesitation against COVID-19 vaccines.

Material and Methods

Study design

A cross-sectional study was conducted at Izmir Health Sciences University Tepecik Training and Research Hospital between 16th November and 31st December 2021. A survey was applied to both parents face to face, which included questions about their sociodemographic characteristics, family members or close relative history of COVID-19 infection and death due to COVID-19, COVID-19 vaccination status of themselves, and their child, the reason if they were not vaccinated, and information sources about COVID-19 disease and vaccines.

The study was approved by the Izmir Health Sciences University Tepecik Training and Research Hospital Ethics Committee (Decision Number: 2021/10-40). An informed consent form was obtained from the participants before initiating the study.

Participant definitions

Parents of children aged 12-18 years who applied to the pediatrics outpatient clinic for any reason, who agreed to participate in the survey, were included in the study. Parents who refused to participate were excluded. COVID-19 vaccination was still available for people aged 12 and up at the time of the study. For this reason, parents with a child between the ages of 12 and 18 were included in the study.

Sample size

The sample size was calculated using $n = Z^2 P (1 - P)/d^2$.[9] Using a 0.05 margin of error with a 95% confidence interval [CI] and 50% response distribution, the calculated minimum sample size was 352.

Statistical analysis

We performed the statistical analysis with the statistical software SPSS version 24.0 (IBM Corporation, Armonk, NY, USA). Demographic and clinical data were analyzed descriptively

and reported as proportions of total patients. The mean ± standard deviation or median and range (minimum value-maximum value) were used depending on whether the data were parametric or not. Comparisons for categorical variables were made using the Pearson chi-square test.

In the statistical analysis, the parent's educational level was based on years of schooling and divided as lower educational level (i.e., 8 years or less), medium educational level (i.e., 9–12 years), and higher educational level (i.e., more than 12 years of education). Household income was divided into three groups according to our country's monthly minimum wage. Accordingly, the minimum wage and below were determined as low income (≤$300), up to twice as medium income ($300-600), and more than twice as high income (>$600).

Child vaccination status was analyzed in two groups:

1-Vaccination acceptance; already vaccinated or willing to be vaccinated.

2-Vaccination non-acceptance; unvaccinated and unwilling to be vaccinated.

Variables with $p<0.25$ value were included in the binary logistic regression model to compare vaccination non-acceptance for the child in univariate analyses. The Backward Wald method was used as the elimination method to determine the essential variables in the final model. According to the Hosmer Lemeshow goodness-of-fit test result for the final model, the model was suitable for the data (χ^2=8,666; p=0.278). A statistical significance level was accepted as $p<0.05$ in the study.

Results

Participant characteristics

Three hundred and ninety-six parents participated in the study. While the median age of the mothers was 40 (28-66) years, the median age of the fathers was 44 (30-75) years. The median age of children was 15 (12-18).

More than 50% of parents had eight years of education or less, and 48.5% had a low household income. Eight percent of the participants consisted of healthcare workers.

Only 11.4% of the children had a history of COVID-19, while 58.1% of the participants had a history of a family member or friend infected with SARS-CoV-2. In addition, 43 (10.9%) participants reported death of a family member or friend due to COVID-19. Thirty-five (8.8%) participants had previous hesitations about routine childhood vaccinations. Also, 44.9% of parents stated that they were worried that their child would be infected with SARS-CoV-2 at school. When people surveyed were asked where they got information about COVID-19 and vaccines, the most common response was 82.1% via television or radio, followed by the internet (65.2%) and social media (48.0%).

Detailed descriptive features of the participants are displayed in Table I.

COVID-19 vaccination status and attitudes

In the study, both parents' vaccination rate with at least one dose of the COVID-19 vaccine was 84.8%. Neither parent in twenty-four (6.1%) couples had ever been vaccinated against COVID-19 (Table II). When each of the parents were evaluated separately, 88.6% of the mothers and 90.2% of the fathers had at least one dose of the COVID-19 vaccine. Among parents who were not vaccinated for COVID-19, the most common reasons were concerns about the vaccine's side effects and doubts about its safety (75.6% of mothers, 69.3% of fathers). Besides, 11.1% of unvaccinated mothers and 10.3% of unvaccinated fathers stated that they were waiting for a domestic COVID-19 vaccine to be vaccinated.

The vaccination rate with at least one dose of the COVID-19 vaccine was only 46.0% in children. Among children who received at least one dose of the COVID-19 vaccine, 55.5% were

Table I. The participants' sociodemographic characteristics and COVID-19-related features.

Variables (n = 396)	n	(%)
Mother age		
Median (min-max), year	40 (28-66)	
≤ 35 years	51	(12.9)
36–50 years	321	(81.1)
> 50 years	24	(6.1)
Father age		
Median (min-max), year	44 (30-75)	
≤ 35 years	15	(3.8)
36–50 years	316	(79.8)
> 50 years	65	(16.4)
Child age		
Median (min-max), year	15 (12-18)	
12-15 years	244	(61.6)
16-18 years	152	(38.4)
Mother education level		
Low	242	(61.1)
Medium	114	(28.8)
High	40	(10.1)
Father education level		
Low	232	(58.6)
Medium	125	(31.6)
High	39	(9.8)
Household income		
Low	192	(48.5)
Medium	144	(36.4)
High	60	(15.2)
Mother or father healthcare worker		
Yes	32	(8.1)
No	364	(91.9)
Child history of COVID-19		
Yes	45	(11.4)
No	351	(88.6)
A family member or friend history of COVID-19		
Yes	230	(58.1)
No	166	(41.9)
A family member or friend death due to COVID-19		
Yes	43	(10.9)
No	353	(89.1)
Other childhood vaccination hesitation		
Yes	35	(8.8)
No	361	(91.2)
Anxiety when sending to school for fear of COVID-19		
Yes	178	(44.9)
No	201	(50.8)
Not attend school	17	(4.3)
Information resources about COVID-19 and vaccines (Multiple Options)		
Television or radio	325	(82.1)
Internet	258	(65.2)
Social media	190	(48.0)
Healthcare professional	157	(39.6)
Friend or close relative	100	(25.3)
All	43	(10.9)

COVID-19: Coronavirus Disease 2019

Table II. Parents' COVID-19 vaccination status and attitudes to vaccinate their children.

	Parental vaccination attitudes						*p*
	Acceptance		Non-acceptance		Total		
	n	(%)*	n	(%)*	n	(%)*	
Both vaccinated**	218	(55.0)	118	(29.8)	336	(84.8)	
Only one vaccinated**	10	(2.5)	26	(6.6)	36	(9.1)	<0.001
Both unvaccinated	3	(0.8)	21	(5.3)	24	(6.1)	

* Percentage by the total number of parents, ** Receipt of ≥1 COVID-19 vaccine dose, COVID-19: Coronavirus Disease 2019

older than 15 years. When parents who had not yet vaccinated their child against COVID-19 were asked whether they were considering vaccinating their children, 12.3% said they were, whereas 41.7% said they were not. Accordingly, COVID-19 vaccine acceptance (vaccinated or willing to be vaccinated) for children was 58.3%. Concerns about the side effects of the COVID-19 vaccine (29.7%) and their children not wanting to be vaccinated (29.0%) were most common, followed by doubts about the safety of the vaccine (15.8%). The reasons parents are hesitant to vaccinate their children and themselves are summarized in Fig. 1.

There was no statistically significant difference between vaccination acceptance and non-acceptance for children, mother and father education level, household income level, or other childhood vaccination hesitation (p = 0.442, p = 0.743, p = 0.294, p = 0.611, respectively).

According to binary logistic regression analysis, mothers under 35 years of age were 6.5-fold (p = 0.002, 95% CI: 2.0-23.1) more likely not to have their children vaccinated than mothers over 50 years of age. Also, in children aged 15 and younger, the rate of not being vaccinated was 2.3-fold (p = 0.001, 95% CI: 1.4-3.7) higher than in those aged 16 and over. It was 3.3-fold (p = 0.026, 95% CI: 1.1-8.0) more common for non-healthcare workers not to have their children vaccinated than healthcare workers. The rate of not vaccinating the children of those whose

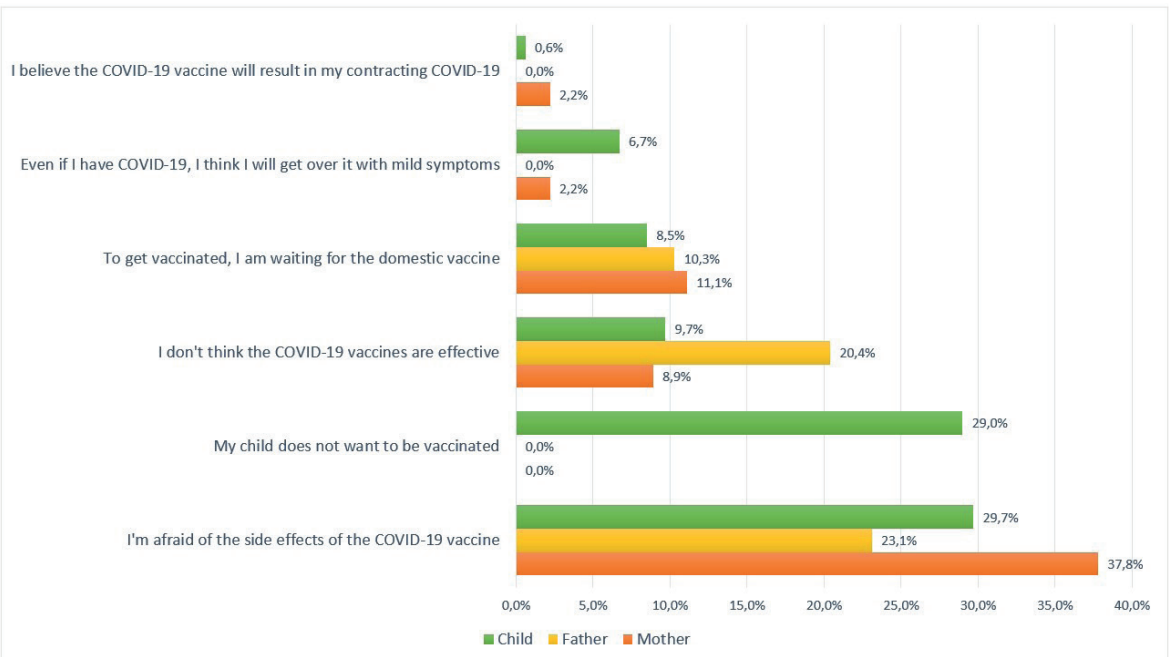

Fig. 1. Reasons why parents were refusing to get COVID-19 vaccinations for themselves and their children.

family members or friends did not have a history of COVID-19 was found to be 1.9-fold (p = 0.006, 95% CI: 1.2-3.0) more than in those with a history (Table III).

According to the vaccination status of the parents, the rate of not vaccinating the children when both parents were unvaccinated was 12.8-fold (p < 0.001, 95% CI: 3.5-46.5) higher than that of both vaccinated parents, and the rate of not vaccinating their children with only one vaccinated parent was 2.2-fold (p < 0.001, 95% CI: 2.2-11.3) higher than that of both vaccinated parents (Table III).

As a result, according to Wald statistics, it can be said that the most influential factor for children not accepting COVID-19 vaccines was "both parents being unvaccinated" (Table III).

Discussion

In our study, parents' rates of not accepting the COVID-19 vaccine for their children was 41.7%. While COVID-19 vaccines were not yet available, in three of the studies conducted in our country, the willingness of parents to have their children vaccinated was reported as 10.4%, 36.3%, 73.9%.[10-12] In the other two studies with conditional vaccination willingness rates, the acceptance rate increased from 38.4% to 41.9% when the vaccine was free, and the acceptance rate was higher for parents' domestic vaccines (56.8%) compared to foreign vaccines (28.9%).[13,14] A striking feature in some of this research is that the rate of parents who stated that they were undecided was between 24-48%, which was close to the acceptance rate.[11-13] Also, unlike our survey, it was seen that the majority of the participants

Table III. Multivariate binary logistic regression of risk factors that cause parents not to vaccinate their children for COVID-19.

	β	S.E.	Wald Statistics	p	Exp (β)	95% C.I. for exp (β)	
						Lower	Upper
Constant	-3.253	0.739	19.386	<0.001	0.039		
Mother age distribution							
> 50 years	Reference						
≤ 35 years	1.925	0.622	9.577	0.002	6.582	2.025	23.184
36–50 years	0.668	0.536	1.558	0.212	1.951	0.683	5.574
Child age distribution							
16-18 years	Reference						
12-15 years	0.835	0.242	11.874	0.001	2.305	1.433	3.706
Mother or father healthcare worker							
Yes	Reference						
No	1.111	0.498	4.982	0.026	3.037	1.145	8.054
A Family member or friend history of COVID-19							
Yes	Reference						
No	0.643	0.235	7.479	0.006	1.902	1.200	3.014
Parents vaccinated status							
Both vaccinated	Reference						
Both unvaccinated	2.554	0.657	15.619	<0.001	12.853	3.548	46.561
Only one vaccinated	1.617	0.413	15.326	<0.001	2.242	2.242	11.320

Variables entered on step 1: Mother age distribution, father age distribution, child age distribution, mother or father healthcare worker, child history of COVID-19, family member or friend history of COVID-19, family member or friend lost due to COVID-19, parents vaccinated status.
Nagelkerke R Square= 0.258, COVID-19: Coronavirus Disease 2019

in the survey had a higher education level and included a higher percentage of healthcare workers. Therefore, these studies are more limited than ours in terms of reflecting the generality of our country. Another point was that the vaccination acceptance rate of parents for themselves was between 49-62%, which was relatively low compared to our study.[10,11,13,14] The socioeconomic consequences of COVID-19-related restrictions and increased reliance on vaccines over the past year may have contributed to vaccine acceptance among parents.

The COVID-19 vaccine willingness rate of parents for their children under 18 has shown a wide range from 17.2% to 91.6% in national surveys in other countries.[15-42] On the other hand, in a study conducted in 16 countries, the acceptance rate of the COVID-19 vaccine for their children was 69.2%, while in another international study with participants from six countries, it was 65.2%.[43,44] As in our research, studies investigating the vaccination acceptance rate for the children of parents with children aged 12-18 was reported as 74.5% in Italy, 83.1% in the United States, and 84.1% in Singapore.[45-47] The differences in results may be related to many factors, including the socio-cultural characteristics of the survey population.

In our investigation, mothers under 35, parents of children aged 15 and under, those with no history of COVID-19 in family members or friends, and non-healthcare workers were the least willing to vaccinate their children. Cross-sectional international and national studies in various countries reported that young parents were more concerned about potential adverse effects and had lower vaccine acceptance rates for their children.[22-24,35,41,43] Other age-related differences in vaccine acceptability between the under 35 and over 50 age groups may be due to the fact that the under 35 generation rarely witnesses deaths from vaccine-preventable diseases compared to those aged 50 and over. In contrast, the results of a survey of more than 3000 women of reproductive age in China revealed that COVID-19 vaccine refusal was higher in women over the age of 45.[41]

Our study found that parents are less willing to get their children vaccinated if they are younger, which is in line with other similar studies.[22,25,35,38,42,43,45,48] This is probably related to parents' perception that young children are more susceptible to vaccine side effects.[34] In our country, COVID-19 vaccination appointments for children aged 12 and older can only be made online with the approval of their parents. However, adolescents over the age of 15 can make their appointments without parental approval. This may have contributed to the vaccination rate in children over the age of 15 being higher than in children aged 15 and under. Parents with a family or friend's history of being infected with SARS-CoV-2 showed a greater intent to vaccinate their children against COVID-19, reflecting a similar observation in two other studies.[11,42]

Our study results revealed a strong correlation between a parent's vaccination status and refusal to vaccinate their child, consistent with other studies.[11,18,42,48] According to all these results, parents' hesitation about vaccination deprives children of their right to vaccinations and causes a decrease in vaccination rates. Revealing the reasons for the refusal of parents and providing accurate information about vaccines will increase the vaccination rates of both parents and children against COVID-19.

The primary concerns reported by parents were the side effects and the vaccine's safety. Various studies on the acceptance of COVID-19 vaccines have shown that the main concerns of parents for vaccines are safety and effectiveness.[49] Parental concerns aside, one-third of parents of unvaccinated children said that their child did not want to be vaccinated. In studies evaluating adolescents' attitudes towards the COVID-19 vaccine, the intention to be vaccinated was found to be 39-51.7%.[46,50,51] It has also been determined that adolescents have a higher intention to be vaccinated if their parents or peers have been immunized with COVID-19

vaccines.[50,51] In this case, there is a need to investigate how often adolescents willing to get the COVID-19 vaccine face barriers and whether parental consent requirements limit their access to vaccines.

The internet and social media remain essential components of sharing health-related information sharing.[52,53] While the internet and social media are instrumental in accessing information, unverified misinformation on these platforms can lead to anti-vaccine attitudes. In our study, the participants explained that they mostly got information about COVID-19 and their vaccines from television, radio, the internet, and social media. Previous research has shown that parents who encounter positive news on social media are more willing to let their children get the COVID-19 vaccine.[11,26] It is clear that social media should be included in approaches to eliminate parents' hesitance about vaccination and increase children's vaccination rates. The rate of getting information from healthcare professionals was only 39.6%, and it was in fourth place. A survey of parents' vaccine safety information resources showed that pediatricians are one of the most reliable sources for vaccines.[54] Therefore, our most important duty as pediatricians is to keep the parents of our patients informed concerning vaccine safety and efficacy.

There are several strengths and limitations to our study. This is one of the few studies that has evaluated parents' attitudes towards vaccinating their children against COVID-19 after approved vaccines for children aged 12-18. In addition, previous research found that mothers were significantly less likely to be willing to vaccinate their children against COVID-19.[23,46,49] Because both parents were interviewed, our findings better reflect the current attitudes of parents than previous studies. However, since this research was conducted in only one region of Türkiye, it has limitations in reflecting the situation throughout the country. Nevertheless, the rate of at least two doses of COVID-19 adult vaccination (86%) in the province of Izmir, where the research was conducted, is similar to the general average in Türkiye.[2] Another limitation was that when evaluating parents' attitudes towards vaccinating their children for COVID-19, we did not assess their COVID-19 anxiety levels. Therefore, we could not evaluate the effect of this condition on vaccine acceptance.

We discovered that 41.7% of children will not be vaccinated because their parents are concerned about COVID-19 vaccination. Our results from the study suggest that providing evidence of the safety of vaccines and informing parents and adolescents of the importance of vaccination can help increase the acceptability of the COVID-19 vaccine.

Ethical approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Izmir Health Sciences University Tepecik Training and Research Hospital Ethics Committee (Decision Number: 2021/10-40). An informed consent form was obtained from the participants before initiating the study.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: AKA, AK, EKO, DY; data collection: AS, BA, YEK, GU, AET, AAM, Gİ; analysis and interpretation of results: AKA, FE; draft manuscript preparation: AS, AKA. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

COVID-19 vaccine hesitancy of adolescents with psychiatric disorders and their parents: data from a child psychiatry outpatient clinic

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ABSTRACT

Background. Vaccinating adolescents and determining the factors influencing their vaccination status are critical in the event of a pandemic. One of the factors affecting vaccination is vaccine hesitancy, which is an increasing problem worldwide. Vaccine hesitancy and the vaccination rates of some special groups, such as psychiatric patients and their families, may differ from the general population. The purpose of this study was to identify any vaccine hesitancy to the coronavirus disease 2019 (COVID-19) vaccination in adolescents evaluated in a child psychiatry outpatient clinic, as well as to determine the factors influencing vaccination in these adolescents and their families.

Methods. Two hundred forty-eight adolescents examined in the child psychiatry outpatient clinic were evaluated using a semi-structured psychiatric interview, strengths and difficulties questionnaire (SDQ), the fear of COVID-19 scale, and a form about coronavirus vaccine hesitancy. The parents completed the vaccine hesitancy scale and answered the vaccine hesitancy questions.

Results. The vaccination rate was higher in patients with anxiety disorders. The patient's age (odds ratio [OR]:1.59; 95% confidence interval [CI]:1.26, 2.02), the parent's vaccine hesitancy (OR: 0.91; CI:0.87-0.95), the status of chronic disease in a family member (OR: 2.26; CI:1.10, 4.65), and the vaccination status of the adolescent's parents (OR:7.40; CI:1.39, 39.34) were found to be predictive for adolescent vaccination. While 2.8% of the adolescents said that they were definitely against getting vaccinated, 7.7% were undecided. While the rate of undecided parents was 7.3%, those who were against vaccination was 1.6%.

Conclusions. Age, parental vaccine hesitancy, and parental vaccination status can affect the vaccination of adolescents admitted to a child psychiatry clinic. Recognizing vaccine hesitancy in adolescents admitted to a child psychiatry clinic and in their families is beneficial for public health.

Key words: vaccination, vaccine hesitancy, adolescent, COVID-19.

Vaccine hesitancy is an important public health problem observed worldwide, including countries that have achieved high immunization rates with high levels of vaccination.[1] According to the World Health Organization (WHO), vaccine hesitancy, despite the presence of a vaccination service, is a complex concept that includes the delay and rejection of a vaccine, which may be affected by the vaccine, by time, and by context.[2] Vaccine hesitancy runs on a continuum ranging from acceptance of the vaccine to complete rejection of all vaccines and there are complex interactions between political, cultural, social, and individual factors about vaccinations.[3] Many reasons can be listed for vaccine hesitancy. These reasons include concerns about the safety of the vaccine, concerns about severe side effects, distrust of the healthcare system, thoughts on vaccine ineffectiveness, misinformation, and social myths.[2,4]

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In the SAGE Working Group Vaccine Hesitancy Determinants Matrix, factors influencing vaccine hesitancy are classified into three categories: contextual, individual and group, and vaccine/vaccination specific influences.[5] Socioeconomic, religious, political and cultural effects are defined as contextual factors, while factors such as vaccine safety, risks and benefits, and cost are classified as features directly related to vaccination. Features such as knowledge, awareness, beliefs about health, characteristics of family members, and personal experiences are defined as individual and group influences.[5]

The concept of vaccine hesitancy, which has become more prominent as a result of the erroneous association between the measles mumps rubella (MMR) vaccine and autism[6] worldwide, as well as claims that some toxins in vaccines cause hyperactivity[7] and false beliefs about the interaction between vaccines and autism[8,9], has been brought to the forefront even more with the coronavirus disease 2019 (COVID-19) vaccination in the pandemic.

The Centers for Disease Control and Prevention (CDC) recommends that everyone aged five years or older should be vaccinated for COVID-19 for protection.[10] Therefore, factors related to child and adolescent vaccination came to the fore during the pandemic.

Adolescents' vaccine hesitancy and vaccine acceptance are complex issues that not only concern themselves but also their parents. In the decision to accept the vaccine, the characteristics of adolescents such as their cognitive development, their peer relationships, risky behaviors, and independence from their parents may be effective.[11] The factors that affect the vaccine hesitancy of parents are concerns about vaccine safety and the possible side effects of the vaccine.[12] In various studies, the COVID-19 vaccine acceptance rate of parents or the rate of parents willing to vaccinate their children was reported as 72.6% in China[13], 82.1% in Italy[14], 55.5% in the USA[15], and 36.3% in Türkiye.[16] Adolescent vaccine acceptance rates were 51.7% in the USA[15], 62.7% in France[17], and 49.6% in Korea.[18] In a study in Türkiye, 43.5% of the adolescents who were examined in the pediatric outpatient clinic were vaccinated against COVID-19 and 27.4% did not want to be vaccinated.[19]

Psychiatric patients are one of the risk groups for vaccine hesitancy and vaccine acceptance, and it was seen that the data related to the effect of psychiatric disorders on vaccine hesitancy and the acceptance of the COVID-19 vaccination were contradictory. It was found that vaccine acceptance changed in patients with psychiatric disorders[20], and vaccine hesitancy was high in severe psychiatric patients.[21] It was also found that COVID-19 vaccine hesitancy was higher in adults with psychiatric disorders such as depression, anxiety disorders, post-traumatic stress disorder, and attention deficit and hyperactivity disorder (ADHD).[22] Additionally, higher vaccine hesitancy levels were related to depression and peritraumatic stress and anxiety.[23] However, there are also some studies with adults that showed that psychiatric disorders did not affect vaccination status.[24,25] In a study involving only inpatient adolescents, it was stated that the vaccination rates were similar to the vaccination rates in the general population.[26]

Based on the literature, it is thought that it is important to reveal the vaccination status and vaccination hesitancy levels of adolescents with psychiatric diseases. Studies evaluating vaccine hesitancy towards the COVID-19 vaccination in adolescents evaluated in an outpatient clinic and their families have not been found. This study aimed to determine the vaccine hesitancy and some individual and family factors that may affect the vaccine hesitancy of adolescents and their families evaluated in an outpatient clinic. Secondly, it aimed to determine some sociodemographic, individual and familial characteristics that may predict the vaccination of an adolescent evaluated in an outpatient clinic. Lastly, the study compared the vaccination status of adolescents diagnosed with a psychiatric disorder and adolescents with typical development who applied for counseling

in a psychiatry clinic with adolescents who did not have a psychiatric diagnosis.

Material and Methods

Procedure and Data Collection

This was a cross-sectional study of adolescents between the ages of 12 and 18 years who were admitted to the Child and Adolescent Psychiatry Outpatient Clinic of Gülhane Training and Research Hospital. After obtaining approval from the ethics committee, 380 adolescents who were examined between November 2021 and January 2022 were reached. The adolescents with missing forms, with an intellectual disability, who were illiterate, with an acute psychotic disorder, or whose parents or themselves did not provide written or verbal consent to participate were excluded from the study. Thus, 248 adolescents with written consent from both themselves and their parents were included in the study. The parents were asked to fill out a sociodemographic data form, answer questions about the COVID-19 vaccine, and complete the vaccine hesitancy form. Adolescents filled out the Fear of Coronavirus questionnaire and provided their thoughts on the COVID-19 vaccine. The Fear of COVID-19 Scale was administered to adolescents to assess their fear of coronavirus at the time and before the discovery and availability of the vaccine. Using this information, the study aimed to compare fear in the pre-vaccination and post-vaccination periods.

Measurements

Sociodemographic Data and Vaccine Hesitancy Assessment Form: From the reviewed literature, COVID-19 vaccine hesitancy was evaluated with the questionnaires developed by the researchers[13,27,28] and so, in line with this literature, questions were prepared by the researcher for the evaluation of the vaccine hesitancy in the present study. The study participants were asked about their age and the ages of their parent(s), their educational status, their opinion on vaccination for their families and the whole society, their reasons for not being vaccinated, whether the family had contracted COVID-19, and whether there were hospitalizations or losses in the family because of COVID-19. The form was filled out by both the adolescent and their parents. All participants were asked, "What do you think about the COVID-19 vaccination?" and "What do you think about family members getting the COVID-19 vaccination?". A choice was made between 'definitely should be vaccinated', 'vaccination may be optional', 'only those in the risk group should be vaccinated', 'I am undecided', and 'definitely should not be vaccinated'. Additionally, "What is the most important reason not to get vaccinated?" and "What is the most important reason to get vaccinated?" were asked.

Vaccine Hesitancy Scale: The Vaccine Hesitancy Scale, which was developed by Kılınçarslan et al.[29] who performed its validity and reliability, is a 5-point likert type scale consisting of 12 items with a 3-factor structure. The Cronbach alpha internal consistency coefficient was 0.85.[29] The Vaccine Hesitancy Scale has three subscales.

The Benefit and Protective Value of the Vaccine Subscale: This subscale evaluated the positive features of the vaccine, was scored inversely, and an increase in these scores was associated with vaccine hesitancy.[29]

Vaccine Repugnance Subscale: This scale assessed the vaccine's negative consequences and side effects, as well as ideas about vaccine companies. An increase in these scores was associated with vaccine hesitancy.[29]

Solutions for Non-vacination Subscale: This subscale evaluated people's opinions about not vaccinating themselves and their children, and an increase in these scores was associated with vaccine hesitancy.[29]

Fear of COVID-19 Scale (FCV-19S): This 5-point Likert-type scale consisting of seven items was developed by Ahorsu et al.[30], and its Turkish validity and reliability study for

adults was completed by Bakioğlu et al.[31] The validity and reliability study for children and adolescents was completed by Gozpinar et al.[32] The Cronbach alpha internal consistency coefficient of the unidimensional scale was 0.88. It is a single factor scale that was added to the study to determine the coronavirus fear levels of the adolescents participating in the study.

Strengths and Difficulties Questionnaire-Adolescent Form (SDQ-A): The scale, developed by Goodman[33], has a self-report structure and its Turkish validity and reliability study was conducted by Güvenir et al.[34] on Turkish children aged 11-17 years. The scale has five subscales and the internal consistency coefficients range from 0.22 to 0.73.[34] It was added to the study to determine and adjust the internalizing and externalizing properties psychologically.

The Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): It was developed as a semi-structured interview for the evaluation of psychopathology in school age children[35] and was adapted according to DSM 5.[36] Ünal et al.[37] confirmed the validity and reliability of this version. It was included in the study to determine psychiatric diagnoses using a semi-structured interview.

Statistical analysis

The IBM SPSS software package program (version 21.0) was used for statistical analysis. (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) The Kolmogorov-Smirnov test was used to test the normality analysis. The statistical significance level was selected as 0.05. The chi-squared test and the independent t test were used when appropriate assumptions were met. The Mann-Whitney U test was used when the necessary assumptions were not met. Fear of coronavirus before and after the availability of the vaccine for adolescents was analyzed with the paired samples t test. Backward binary logistic regression analysis was performed to determine the predictive factors in the vaccination of adolescents. The final logistic regression model was created by including the factors reported to be effective in the vaccination of adolescents in the literature, psychological factors and the variables obtained by adding the variables found to be significant in the basic statistics in this study. Age, gender, hospitalization due to COVID-19, death due to coronavirus in the family of the adolescent, chronic disase in the family member, externalizing score, internalizing score, educational status of parents, fear of coronavirus before and after the discovery of the vaccine, psychiatric diagnoses, and the parents' vaccine hesitancy scores were analyzed using backward logistic regression analysis to determine the factors that predict the vaccination of adolescents.

Results

Sociodemographic data

Adolescents aged 12-18 years were included in the study and the median age of the participants was 15 years (interquartile range[IQR]=2). Among the adolescents, 174 (70.2%) were female, and 74 (29.8%) were male. Of the adolescents, 46.8% (n=116) were vaccinated with one of the COVID-19 vaccines. Two hundred seventeen (88.2%) parents stated that they were vaccinated. The sociodemographic data of the vaccinated and unvaccinated adolescents are shown in Table I.

No statistical difference was found between vaccinated and unvaccinated adolescents in terms of being infected with COVID-19 themselves (p=1.000) or their family members (p=0.824) at any time, but the rate of vaccination was statistically significantly higher in the adolescents with a family history of chronic diseases (p=0.008) and those whose family member died (p=0.01) due to COVID-19. Further details about the data are presented in Table I.

While the fear of coronavirus mean score was 14.43 (standard deviation [SD]=6.40) before the development of the vaccine, it was 12.99

Table I. Sociodemographic data of vacinated and unvacinated adolescents.*

	Vacinated Adolescents	Unvacinated Adolescents	P
Age	15.0 (3.0)	14.0 (3.0)	<0.001
Gender			0.315
female	85 (73.3)	89 (67.4)	
male	31 (26.7)	43 (32.6)	
Maternal education			0.061
Not graduating high school	42 (40.0)	63 (60.0)	
High school graduate or higher	55 (51.4)	52 (48.4)	
Paternal education			0.08
Not graduating high school	34 (38.6)	54 (61.4)	
High school graduate or higher	60 (50.8)	58 (49.2)	
Monthly income			0.639
<2500 TL	17 (14.8)	25 (19.2)	
2500-8000 TL	85 (73.9)	90 (69.2)	
>8000 TL	13 (11.3)	15 (11.6)	
Parents			0.001
Vacinated	110 (95.7)	107 (81.7)	
Unvacinated	5 (4.3)	24 (18.3)	
COVID-19 history in a family member			0.824
Yes	59 (50.9)	59 (47.7)	
No	57 (49.1)	63 (52.3)	
Hospitalization of a family member due to COVID-19			0.174
Yes	17 (14.7)	12 (9.1)	
No	99 (85.3)	120 (90.9)	
Death of a family member due to COVID-19			0.010
Yes	10 (8.6)	2 (1.5)	
No	106 (91.4)	129 (98.5)	
Chronic disease of a family member			0.008
Yes	49 (45.4)	35 (28.5)	
No	59 (54.6)	88 (71.5)	
COVID-19 history of the adolescent			1.000
Yes	29 (25.0)	33 (25.0)	
No	87 (75.0)	99 (75.0)	

*Data are presented as n (%), except for age (in years), presented as median (interquartile range).

(SD=6.30) after the vaccine became available, and it decreased statistically significantly (paired samples test; p<0.001). When the coronavirus fear scores of vaccinated (mean±SD=12.82±6.27) and unvaccinated (mean±SD=13.15±6.34) adolescents were compared, no significant difference was found (independent t-test; p=0.68).

Vaccine Hesitancy

All adolescents that participated in the study answered the vaccine hesitancy questions. Of the adolescents, 47.8% thought that they should definitely be vaccinated for the benefit of society, and 52.8% said that they should definitely be vaccinated when they answered these questions for their own families. Whereas, 2.8% of the

adolescents stated that they were definitely against getting vaccinated considering the benefit to society, and 1.6% stated that their families thought that they definitely should not be vaccinated. A small number of parents (1.6%) stated that they were definitely against getting vaccinated considering the benefit to society, and 2% stated that their families thought that they definitely should not be vaccinated. The thoughts of the adolescents and their parents are presented in detail in Table II.

Eighty-four adolescents (49.1%) and ninety (50%) parents answered that there was no valid reason to the question concerning the most important reason not to be vaccinated. In the group that thought that there was a reason not to be vaccinated, side effects were the most frequently cited reason (for adolescents: 36.3%; n=62; for parents: 28.3%; n=51). Uncertainty about the effect of the vaccine and insufficient studies were the second most common reason (for adolescents: 21.7%; n=39; for parents: 14.6%; n=25).

When the vaccine hesitancy questionnaire scores of the parents were compared according to whether their children were vaccinated or not, the total score of vaccine hesitancy (p<0.001), solutions for non-vaccination (p<0.001), the benefit and protective value of the vaccine (p<0.001), and the vaccine repugnance scores (p<0.001), were statistically higher in the group whose children were not vaccinated (Table III). When the vaccine hesitancy questionnaire scores of the parents were compared according to whether their children had a psychiatric disorder or not, the total score of vaccine hesitancy (independent t-test, p=0.346), solutions for non-vaccination (Mann-Whitney U test, p=0.247), the benefit and protective value of the vaccine (Mann-Whitney U test, p=0.557), and the vaccine repugnance scores (Mann-Whitney U test , p=0.532), were not significantly different between the groups.

Psychopathology

The diagnosis of psychopathology was made using semi-structured psychiatric interviews and clinical examinations. The vaccination rate was 49.5% in adolescents with psychiatric disorders, and 30.6% in those without. A statistically significant difference was found between the vaccinated and unvaccinated adolescents in terms of psychiatric diagnoses (p=0.047). Adolescents with an anxiety disorder were vaccinated statistically significantly more (p<0.001) (Table IV).

Table II. Parents and adolescents' thoughts about vaccination.

	For the public n (%)	For their family n (%)
Thought of adolescents about vaccination		
Definitely should be vaccinated	118 (47.8)	130 (52.6)
Vaccination should be optional	94 (38.1)	84 (34.0)
Vacination for the risk group only	9 (3.6)	7 (2.8)
Undecided	19 (7.7)	22 (9.0)
Definitely against vaccination	7 (2.8)	4 (1.6)
Thought of parents about vaccination		
Definitely should be vaccinated	154 (62.9)	157 (63.8)
Vaccination should be optional	62 (25.3)	64 (26.0)
Vacination for the risk group only	7 (2.9)	5 (2)
Undecided	18 (7.3)	15 (6.1)
Definitely against vaccination	4 (1.6)	5 (2)

Table III. Vaccine hesitancy scores of parents of vaccinated and unvaccinated adolescents.

Vaccine Hesitancy Scale Scores	Vacinated Adolescents Median (IQR)	Unvacinated Adolescents Median (IQR)	*p*
Subscale of Benefit and Protective Value of Vaccine	7 (5)	9 (6)	<0.001[a]
Vaccine Repugnance Subscale	12 (5)	14 (5)	<0.001[b]
Solutions for Nonvaccination Subscale	6 (5)	8 (3)	<0.001[b]
Vaccine Hesitancy Total Score	25 (12)	31 (10)	<0.001[b]

[a]Independent t-test, [b]Mann-Whitney U test, IQR: Interquartile range

Table IV. Psychiatric diagnoses of vaccinated and unvaccinated adolescents.

	Vacinated adolescents n (%)	Unvacinated adolescents n (%)
No psychiatric diagnosis	11 (30.6)	25 (69.4)
Depression	17 (44.7)	21 (55.3)
Anxiety disorders	48 (60.8)	31 (39.2)
ADHD	19 (42.2)	26 (57.8)
OCD	7 (36.8)	12 (63.2)
Other diagnosis	14 (45.2)	17 (54.8)

ADHD: Attention deficit and hyperactivity disorder, OCD: Obsessive-compulsive disorder

When the Strengths and Difficulties Questionnaire scores of the vaccinated and unvaccinated adolescents were compared, no significant difference was found in the internalizing (p=0.410), externalizing (p=0.994), prosocial (p=0.278), and total difficulties scores (p=0.599).

Logistic regression analysis

Age, gender, hospitalization due to COVID-19, death due to coronavirus in the family of the adolescent, chronic disease in the family member, externalizing score, internalizing score, educational status of parents, fear of coronavirus before and after the discovery of the vaccine, psychiatric diagnoses, and parent's vaccine hesitancy scores were analyzed using backward logistic regression analysis to determine the factors that predict the vaccination of adolescents (Nagelkerke R^2: 0.39). Age (OR: 1.59; 95% CI: 1.26, 2.02), the parent's vaccine hesitancy (OR: 0.91; 95% CI: 0.87-0.95), chronic disease of the family member (OR: 2.26; 95% CI: 1.10, 4.65), and the vaccination of the parents (OR: 7.40; 95% CI: 1.39-39.34) were determined to be predictive of the vaccination of the adolescents (Table V).

Table V. Predictive variables in adolescent vaccination.

	p	OR	95% CI
Age of the adolescent	<0.001	1.59	1.26-2.02
Parent Vacine Hesitancy Score	<0.001	0.91	0.87-0.95
Parental vaccination	0.019	7.40	1.39-39.34
Chronic disase in the family member	0.027		1.10-4.65

CI: Confidence Interval, OR: odds ratio

Discussion

It has been shown that vaccination rates have decreased in Türkiye and it has been emphasized that one of the most important reasons for this decrease is vaccine hesitancy.[38] Vaccine hesitancy and vaccine refusal, which have increased in importance during the pandemic period, have been investigated in current studies in psychiatric patients.[22,21] This study aimed to investigate the COVID-19 vaccination status, vaccine hesitancy and the factors affecting vaccination in adolescent psychiatric patients. Based on information obtained from adolescents and their parents evaluated in the child psychiatry outpatient clinic, it was determined that 46.8% of the adolescents had been vaccinated at least once, and this rate was 88.2% in their parents. Whether the adolescent was vaccinated or not, if the parents were vaccinated, the lower level of parental vaccine hesitancy, and a chronic disease in family members or the death of a family member due to the coronavirus were all statistically significant results. The vaccination rates among adolescents with anxiety disorders were found to be higher.

In this study, the rate of vaccination was 49.5% in adolescents with psychiatric disorders, 30.6% in adolescents without a psychiatric diagnosis and 88.2% in all parents. As of March 12, 2022, in Türkiye, the rate of a one dose vaccination in adults was reported as 93.01%, and the rate of double dose vaccination was reported as 85.22% according to data from the Ministry of Health.[39] In a study evaluating the adolescent vaccination rates in the age range of 15-18 year olds in Türkiye, this was 43.5%.[19] The vaccination rate of at least one dose among parents was close but lower than the data given by the Ministry of Health. In adolescents with psychiatric disorders, although there is no data from the Ministry of Health, it is close to the data from the study conducted in Türkiye. When the articles of studies conducted in other countries were examined, just a study on adolescent psychiatric inpatients was found. In the study in the USA, it was shown that 30.5% of hospitalized patients were vaccinated with one dose before hospitalization, and 29.8% agreed to be vaccinated during hospitalization.[26] Although there is a partial difference in the present study compared to the data in the USA, the differences between the results may be due to the fact that the studies were conducted at different times of the pandemic and the most common diagnoses of inpatients and outpatients in child and adolescent psychiatry clinics were different.

One of the hypotheses of this study was that the vaccination status would be different in adolescents with different psychiatric disorders. According to the study, the vaccination rate for anxiety disorders was higher than for typically developing adolescents. In the literature, the effect of psychiatric disorders on the COVID-19 vaccination is contradictory. In a previous study, it was reported that there was no difference in vaccination rates for psychiatric disorders.[25] Meanwhile, another study found that vaccination rates were lower in people with severe psychiatric disorders.[40] In contrast, in the present study, the rate of vaccination was higher in adolescents with psychiatric disorders, especially in anxiety disorders. While interpreting the data, it should be considered that the diagnoses in the patient population included in the studies[25,40] are different, These studies were conducted in adults and the most common diagnoses were psychotic disorders, whereas anxiety disorder was the most common in our study, similar to child psychiatry diagnoses in the literature.[41] Anxiety about COVID-19 and concerns about health are shown to be associated with vaccine acceptance[42], but a low fear of COVID-19 has been associated with vaccine hesitancy.[43] Additionally, in a study evaluating vaccine hesitancy in adults with anxiety disorders, intolerance to uncertainty was associated with vaccine hesitancy.[44] Based on these results, it can be thought that adolescents with anxiety disorders may have higher anxiety about the coronavirus infection and efforts to reduce uncertainty may increase vaccination rates.

Determining the vaccination status and hesitancy about vaccination of patients admitted to the psychiatry clinic is a rather complex concept that is not only affected by psychiatric diagnoses. There are sociodemographic, parent-related, and vaccine-related factors that affect vaccine acceptance in adolescents.[45] Similar to studies in adults[46,47], parents' and adolescents' age, gender, educational status, and economic status were related to the acceptance of the COVID-19 vaccine.[45] In this study, the age of the adolescent were also found to be significant. This study revealed that increasing age is an important predictor of vaccination in the adolescent population with psychiatric disorders. Similarly, a meta-analysis including participants over the age of 16 years showed a correlation between increasing age and increasing vaccine acceptance.[48] However, there was an article that did not find a relationship between the vaccination rate and age in adolescents.[49] The reasons for the younger age in the unvaccinated group compared to the vaccinated group may include the low number of studies in young age[50] and, the unpredictability of possible long term side effects in the developing brain and body.

Another influential factor in the vaccination of adolescents may be the thoughts and decisions of the parents. It is complicated whether the parent or the adolescent makes the final decision regarding the adolescent's vaccination.[51] In this study, the factors found to be predictive of the vaccination rate in the patients examined in the child psychiatry clinic were the vaccination of parents and the level of parental vaccine hesitancy. Similar to the present study, it was revealed that the willingness of the parents to vaccinate is related to the adolescent's vaccine acceptance and hesitancy[45] and it was found that vaccination of one or both parents was related to the adolescent's decision to vaccinate.[49]

Adolescent and parent vaccine hesitancy levels were evaluated separately as they may affect each other, and close percentages were found in both adolescents and parents. Of parents, 1.6% were definitely against vaccination, while 7.3% were undecided. The rate of adolescents who were definitely against vaccination was 2.8%, and the rate of those who were undecided was 7.7%. In a study in 2020, it was reported that 31% of parents were undecided and 3% of parents refused to vaccinate themselves and their children against COVID-19 in Türkiye.[52] The rate of parents who refuse the vaccine and undecided parents seems to have decreased. It may be due to the higher awareness of the vaccines among the adolescents and their families included in this study, or it may be due to the fact that this study was conducted more recently. In the literature, concerns about vaccine side effects[53] and uncertainties about vaccine efficacy were associated with higher vaccine hesitancy.[14] The most common reasons for not being vaccinated in this study were side effects and the uncertainty of the effect of the vaccine. Concerns about side effects and uncertainty of long-term effects of vaccines have also been found to be associated with vaccine hesitancy in different countries.[54-56] The increase in COVID-19 vaccination during the pandemic and the increase in knowledge about possible effects and side effects may be the reasons for the lower levels of vaccine hesitancy in this study.

Finally, some family-related factors were found to be important in the vaccination status of the adolescents in this study. The rate of vaccination was higher in adolescents with chronic diseases of family members, and death in their families. Chronic disease in one of the family members was a predictive factor for vaccination. In some studies, one of the most important reasons for vaccine acceptance is not wanting to infect others.[57,58] For this study's participants, it was thought that the concern that the disease would have negative consequences for their family members may have affected their vaccination status.

To the best of our knowledge, this study is the first to evaluate COVID-19 vaccine hesitancy in adolescents examined in an outpatient child psychiatry clinic. The strengths of this study are the evaluation of vaccine hesitancy

opinions of both adolescents and their parents in the vaccination of adolescents and the use of a psychiatric diagnosis using semi-structured interviews.

This study has some limitations. The adolescents examined in the Gülhane Training and Research Hospital and their families were included in the study, so its generalizability to all psychiatric patients and the public is poor. An important limitation is that patients with psychosis and bipolar disorder were not included in the study because during the data collection period there were no adolescents with these diagnoses among those who accepted to participate in the study. In addition, adolescents with intellectual disabilities or autism spectrum disorders were excluded from the study due to illiteracy and the validity and reliability data of the scales could not fully cover these groups. It is important to conduct further research with special study designs for these groups. In this study, adolescents who applied for counseling and showed typical development and those who did not have any psychiatric diagnosis were used as a comparison group, and the control group was not taken from the community. It should be kept in mind that these participants may not reflect community data. Adolescents retrospectively answered questions about their fear of the coronavirus before the discovery of the vaccine, it should be kept in mind that the results may also be affected by memory.

Consequently, in this study, it was found that vaccination of adolescents who applied to the child psychiatry outpatient clinic was associated with age, parental vaccination status, parental vaccine hesitancy, and having a chronic disease in a family member. The rate of vaccination was found to be higher in adolescents with anxiety disorders than in adolescents with typical development. It should not be forgotten that there are some factors that could not be controlled during the study. There are many factors affecting vaccine hesitancy and vaccination; such as COVID-19 mutations and vaccine response, vaccine related-factors, trust in vaccine companies, political and geographic factors, and the role of media.[5] Whether these factors have the same effect on adolescent psychiatric patients and the general population is a subject for further research. It is considered useful to evaluate these factors in further studies.

Determining the COVID-19 vaccination status and vaccine hesitancy of adolescents with mental disorders and their families may contribute to developing strategies during the pandemic and other vaccination policies for specific groups. Additionally, it is thought that mental health professionals can contribute to decreasing vaccine hesitancy by providing appropriate information about vaccine hesitancy or by ensuring that their patients have access to the necessary information. Lastly, studying what teenagers think about vaccines during a time when their individuality is becoming more important could help shape future vaccination policie.

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Ethical approval

This study protocol was approved by the Clinical Research Ethics Committee of Gülhane Faculty of Medicine in 2021 (19.10.2021-2021/12). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written and verbal consent was obtained from all participants and their parents / legal guardians in accordance with ethical standards.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design:

BOA; data collection: BOA, GO; analysis and interpretation of results: BOA,MAC; draft manuscript preparation: BOA, GO, MAC. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Vaccine refusal risk factors among parents of children with autism spectrum disorders

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ABSTRACT

Background. Vaccine refusal is a global trend and was announced as one of the top ten health threats in recent years. The rate of vaccine refusal (VR) among children with autism spectrum disorders (ASD) has also increased in parallel with the global trend but their vaccination behavior may differ from that of the normal population. This study aims to determine the VR rates among parents of children with ASD, to define the risk factors for developing VR, and to evaluate the parental concerns for childhood vaccinations in this susceptible population.

Methods. We conducted a 4-part survey questionnaire among parents of children with ASD, evaluating the vaccination status for both the child with ASD and their younger sibling. The vaccination uptake of the first child was accepted as the 'baseline' behavior, while the following sibling's uptake was suggested as the 'current' behavior. The risk factors of VR were determined with logistic regression analysis.

Results. The study group included 110 parents of children with ASD (M/F:76/34) and their younger siblings (M/F:57/53). The rate of 'baseline VR' was 12.7 % whereas the 'current VR' was 40% (p=0.001). High socioeconomic status (relative risk [RR]: 4.4; 95% confidence interval [CI]: 1.01-16.6; p=0.04), using social media as the main source of information (RR: 7; 95% CI: 1.5-32; p= 0.01) and lack of regular well-child visits of the sibling (RR: 25; 95% CI 4.1-166; p=0.001) were determined as risk factors for VR.

Conclusions. The vaccination behavior of parents changed after having a child with ASD, and thus, the younger siblings may constitute a risk group for VR. In clinical practice, pediatricians should be aware of this risk and evaluate the vaccination uptake of the younger siblings of children with ASD more carefully. Regular well-child visits and improving media literacy may be the key points to prevent VR in this susceptible population.

Key words: autism spectrum disorder, vaccine refusal, childhood, vaccination behavior.

Vaccine refusal (VR) is a growing global trend constituting a substantial threat to reverse the progress made in tackling vaccine-preventable diseases. The World Health Organization (WHO) has announced VR as one of the ten threats to global health by 2019.[1] Since then, the coronavirus disease 2019 (COVID-19) pandemic has arisen and affected vaccination behavior on both ends of the spectrum: increased awareness of vaccination against infectious diseases, especially among the people who accept vaccines, and increased refusal and hesitancy, most probably due to mistrust in novel vaccines.[2] Previous research has shown that newer vaccines generate more hesitancy.[3] To tackle VR and hesitancy, WHO recommends that each country take steps to develop an understanding at a local level on an ongoing basis that differs according to the cultural, societal, and personal beliefs of a particular region in addition to the worldwide needs and concerns.[4]

In Türkiye, although the cases of VR were very few previously and only 180 families refused vaccination in 2011, the anti-vaccination movement has shown a rapid increase in the last 10 years, especially after a public prosecutor

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refused the vaccination of his twin children in 2015. The local court decided that the children should be vaccinated despite the father's refusal, but the Supreme Court decided that vaccination requires "consent from parents for vaccination". The Supreme Court decision was dubbed "the prosecutor father's victory" by the press.[5] Meanwhile the number of VR cases approached 25,000 as of 2018.[6]

It was previously reported that families with children who had ASD were less likely to vaccinate their subsequent children.[7] Compatible with this, younger siblings of children with ASD were reported to have delayed and/or refused vaccination and reduced overall vaccination rates when compared to both the general population and their older siblings with ASD.[8] Parents of children with ASD may be prone to ignore genetic causes of the disorder and instead blame environmental factors for its development. In addition, they may believe in non-evidence-based information about developmental disorders and vaccines. However, there is a lack of knowledge about the reasons and risk factors that cause VR among parents of children with ASD, leading to reduced vaccination rates among the younger siblings.

This study aimed to determine the VR rates among parents of children with ASD, to define the risk factors for developing VR after having a child with ASD, and to evaluate the parental concerns about childhood vaccines in this susceptible population.

Material and Methods

Study design and participants

This was a descriptive study conducted among parents of children with ASD who were being followed up by the Department of Child and Adolescent Psychiatry of İzmir Dr. Behçet Uz Children's hospital which is a tertiary hospital for children. The study was reviewed and approved by the Local Ethics Committee of Behçet Uz Children's Hospital on 08.03.2018 (Protocol no: 2018/196, Decision No: 2018/05-01) and participation involved informed consent.

The diagnosis of the patients and severity levels for the disorder were based on the Diagnostic and Statistical Manual of Mental disorders: DSM-5.[9] The parents were first asked if they had a consecutive child, and if yes, they were asked to participate in the study. The offer to participate in the study was made at the end of their visit to maintain complete volunteerism. The parents whose consecutive child's vaccination schedule was continuing for primary immunisation (<2 years of age), completed before an ASD diagnosis and parents of half/step-siblings were not included in the study. The questionnaire was applied during a face-to-face interview by the researchers.

The survey questionnaire consisted of 4 main parts. The first part included items about socio-demographiccharacteristics. The second part was about the child with ASD (age, gender, severity of the disorder, accompanying disorders, etc) and their vaccine uptake. The third part aimed to evaluate the consecutive child's vaccination uptake, thus including questions about age, gender, any chronic disorders of the child, and the attitude of the parents towards the consecutive child's vaccination.

As the definition of VR includes 'refusal of vaccination despite the availability of vaccination services, only the vaccines that are included in the National Vaccination Program, and thus administered routinely were evaluated in the questionnaire, to ensure their availability. The vaccination uptake of the first child indicated the 'baseline' attitude of the parents for the childhood vaccines, while the consecutive sibling's uptake showed the 'current' attitude, after being a parent of a child with ASD. To have refused any (at least one) of the routinely administered vaccines was accepted as VR. Then, the study group was divided into 2 groups: Group 1 included parents who had developed VR in their current attitude although they were VR (-) in their

baseline attitude; Group 2 included parents who had accepted all vaccines in both baseline and current attitude. The parents who were VR (+) in their baseline attitude were not included in the group comparisons. The schematic diagram of the study design is presented in Fig. 1.

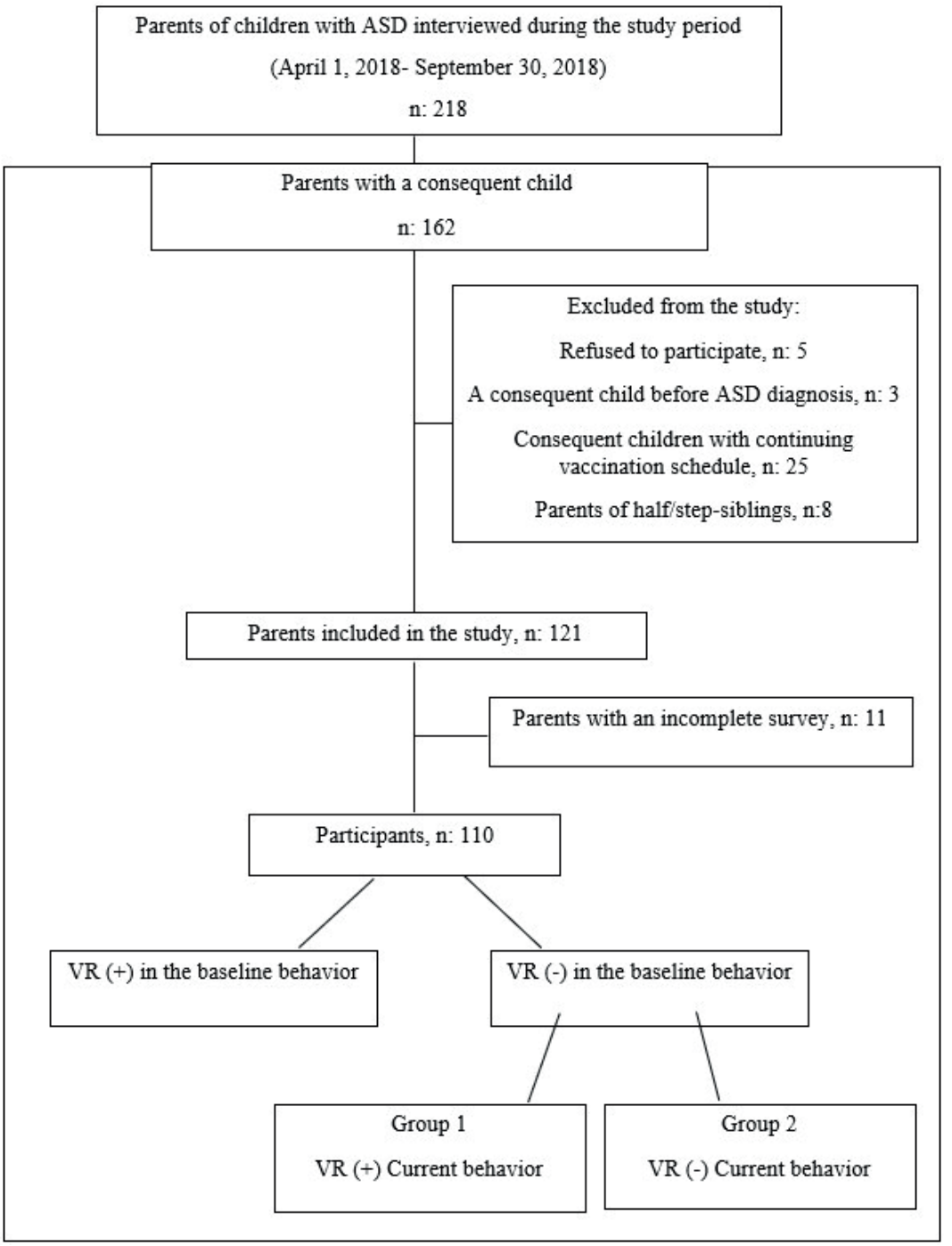

Fig. 1. The schematic diagram of the study design.

The fourth part of the questionnaire was designed to assess the parental concerns about childhood vaccines among all participants. This part included 5-Likert-type items (strongly agree, tend to agree, do not know, tend to disagree, strongly disagree) in addition to open-ended questions where appropriate. Their perception about ASD and relation to vaccines, and thoughts about VR were evaluated with Likert-type questions e.g. 'In my opinion, my child's autism is related to vaccines', 'Vaccine refusal threatens public health', 'In my opinion, parents have the right to refuse routinely administered vaccines'. The answers 'I strongly agree/tend to agree were accepted to be consistent with the statement. The parents who assumed that their child's autism was related to vaccines were also asked about 'which vaccine' and/or 'which component of vaccine' and 'how' it caused autism (open-ended questions).

National Vaccination Program

The National Vaccination Program of Türkiye covers vaccination against diphtheria, tetanus, measles, rubella, mumps, tuberculosis, polio, chickenpox, hepatitis A, hepatitis B, invasive Streptococcus pneumoniae, and invasive Haemophilus influenzae type b in the first 2 years of life and continues with rappel doses in the following years. The current schedule is among the most comprehensive programs with 13 antigens since 2013 and has been updated in 2020 by the Ministry of Health.[10] Table I presents the National Vaccination Program that was being held during the study period (01.04.2018-01.10.2018).

Statistical analyses

The data were analyzed using the Statistical Package for the Social Sciences (SPSS, version 18.0). Categorical data were presented as percentages whereas numerical data with Gaussian distribution were presented as mean ± standard deviation. The Chi-square or Fisher's exact test was used to compare proportions between groups where appropriate. The parameters that were found to be significant in developing VR by univariate analyzes were analyzed with logistic regression analysis. The p-value of <0.05 was considered statistically significant.

Results

The study group included 110 parents (88 mothers and 22 fathers) of 110 children with ASD (M/F:76/34; mean age: 7.2±0.27 years) and 110 consecutive siblings (M/F:57/53; mean age 3.4±0.16 years). The sociodemographic properties of the parents and clinical properties of the children are presented in Table II.

The prevalence of 'baseline' VR was 13% (14/110) in the study group whereas the

Table I. The National Vaccination Schedule of Childhood* during the first 2 years of age.

	Birth	1. month	2. month	4. month	6. month	12. month	18. month	24. month
Hepatitis B	I	I I			I I I			
BCG			I					
DaPT-IPV-Hib			I	I I	I I I		R	
PCV			I	I I		R		
OPV					I		I I	
MMR						I		
Varicella						I		
Hepatitis A							I	I I

* The third dose of conjugated pneumococcal vaccine has been extracted from the schedule by January 2019, thus, the participants were expected to have administered the third dose, at 6 months of age.
BCG: Bacille Calmette Guerine vaccine, DaPT-IPV-Hib: Diphtheria, acellular pertussis, tetanus- Inactive polio vaccine-*Haemophilus influenzae* type b, PCV: Pneumococcal conjugate vaccine, OPV: Oral polio vaccine, MMR: Measles mumps rubella

Table II. The clinical and sociodemographic characteristics of the children and parents (n:110).

Mean age (mean±SD)	
Child with ASD	7.2±0.27
Younger sibling	3.4±0.16
Gender (M/F)	
Child with ASD	76/34
Younger sibling	57/53
Disorder severity of the child with ASD, n (%)	
Requiring support	39 (35)
Requiring substantial support	48 (43)
Requiring very substantial support	23 (20)
Additional diseases of the child with ASD, n (%)	
Mental disorders	46 (41)
Physical chronic disorders	8 (7)
Education level of the mother, n (%)	
Not educated	21 (19)
Elementary school	21 (19)
Middle school	22 (20)
High school	26 (23)
University	20 (18)
Education level of the father, n (%)	
Not educated	13 (11)
Elementary school	27 (25)
Middle school	23 (21)
High school	23 (21)
University	24 (22)
Marital status (Married/Single)	97/13
Socioeconomic status, n (%)	
Very low/low	45 (41)
Middle	23 (21)
High/very high	42 (38)

ASD: autism spectrum disorder

prevalence of 'current' VR was 40% (44/110) and the difference was statistically significant (p<0.001). The frequency of children with no vaccination was 28% (4/14) among baseline VR cases while 31% (14/44) among currentVR cases (p=0.8).

Table III presents the factors related to developing VR in the study group. When we compared Group 1 (n:30) with Group 2 (n:66), the severity of ASD, additional diseases of both children, the gender of the sibling were similar between groups (p=0.13, p=0.12, p=0.13, respectively). However, the frequency of high-income families in Group 1 was 63% while 27% in Group 2 (p=0.001). Moreover, the percentage of parents that graduated from high school and university in Group 1 (68%), was significantly higher than Group 2 (27%) (p=0.02). Only 21% of the parents in Group 1 attended regular well-child visits of the younger child, while the same it was 78% in Group 2 and the difference was significant statistically (p=0.009). The frequency of using new generation media as the main source of information about vaccines was significantly higher in Group 1 than in Group 2 (76% vs 23%; p=0.006). The risk ratios for independent variables show a significant

Table III. The factors related to developing vaccine refusal in the study group.

Total n:96	*Group 1 n: 30	**Group 2 n:66	p
Severe ASD§, n (%)	26 (86)	49 (74)	0.172
Having additional diseases, n (%)	13 (43)	19 (29)	0.16
Male gender (the sibling), n (%)	24 (80)	44 (66)	0.18
High/very high socioeconomic status, n (%)	19 (63)	18 (27)	0.001
High school and higher education level of the mother, n (%)	18 (60)	23 (35)	0.021
High school and higher education level of the father, n (%)	18 (60)	24 (36)	0.03
Regular well-child visits, n (%)	21 (70)	60 (90)	0.009
Using social media as the main source of information, n (%)	23 (76)	15 (23)	0.006

§Severe disease defines the group of children with ASD requiring substantial/very substantial support.
*Group 1 presents the participants who developed VR after being a parent of a child with ASD.
**Group 2 presents the participants who continued to accept all vaccines after being a parent of a child with ASD.
The parents who were VR (+) in their baseline attitude were not included in the group comparisons.
ASD: autism spectrum disorder, VR: vaccine refusal

difference for high-income families, using social media as the main source of information and lack of regular well-child visits of the sibling to develop VR (Table IV).

Opinions and parental concerns about childhood vaccines were evaluated among all participants. The frequency of parents who believe that their child's autism is related to vaccines was 35%. But, when they were asked 'which vaccine' and/or 'which component' might have caused autism, 58% of them confessed that they did not know about this issue. Furthermore, 92% of them stated that they did not know 'how?' vaccines caused autism. Although 87% of participants were aware that VR poses a risk to public health, only 52% considered VR to be a "parental right."

Discussion

The results of this study show that the attitudes of parents changed after becoming parents of children with ASD and the prevalence of VR increased among this susceptible population, affecting the vaccine uptake of the consecutive child. It was previously documented that families of children with ASD were less likely to vaccinate their consecutive children.[7,8,11] But, the literature lacks the risk factors for developing VR among these families. Although it was previously reported that VR is also related to personal negative experiences,[4] according to our results, the severity level of ASD, additional diseases of both children, the gender of the sibling did not affect the risk of developing VR in the study group. However, our results indicate that high-income, using social media as the main source of information and lack

Table IV. The risk factors of developing VR after being a parent of a child with ASD.

	B	SE	OR	%95 CI		p
				Lower	Upper	
High school and higher education level of the mother	1.70	1.09	5.48	0.64	46.80	0.12
High school and higher education level of the father	0.86	1.27	2.32	0.19	2.82	0.49
High/very high socioeconomic status	1.41	0.71	4.11	1.01	16.60	0.04
Using social media as the main source of information	1.94	0.78	7.02	1.52	32.49	0.01
Lack of regular well child visits of the sibling	3.25	0.93	25	4.11	166	0.001

ASD: autism spectrum disorder, B = Coefficient of regression, SE = Standard Error, OR = Odds Ratio, CI = Confidence Interval, VR: vaccine refusal

of regular well-child visits are risk factors to develop VR among parents of children with ASD. To the best of our knowleadge, the current study is the first study to define the risk factors for developing VR among parents of children with ASD.

The relationship between socioeconomic status and vaccine acceptance is controversial. Although a previous systematic review reported lower vaccine uptakes in the general population with lower parental income and lower education level[12], Larson et al.[13] have documented an emerging inverse relationship between vaccine uptakes and socio-economic status in their study conducted among 67 countries. According to our results, the rate of high-income families among participants who developed VR after becoming a parent of a child with ASD was significantly higher than the participants who were not; and this was found to be an independent risk factor for increasing VR in the study group.

Another issue about the global trend of VR is the effect of new generation media including social media. For an increasing number of people, the internet has become the most commonly used source of information about health protection and vaccines.[14] Social media platforms are internet-based applications that enable users to create, interact with, and share content with others with multiple platforms for different types of content. In contrast to traditional media, social media allows individuals to share content rapidly and globally without editorial oversight.[15] Furthermore, on social media, statements on health issues may have a similar effect whether they belong to a medical professional or someone who has no professional interest in health.[16] In the literature, fake news and misinformation on social media have already been reported to be the main causes leading to increasing rates of vaccine hesitancy and VR.[17,18] In addition, on social media, people come across various conspiracy theories about vaccines and may be convinced that alternative therapies instead of modern medicine can provide them with better protection against diseases, as modern medicine is financed by pharmaceutical and vaccine companies.[18-20] Our results support the literature that using new generation media as the main source of vaccine information is a risk factor to develop VR in this susceptible population. However, the current study was conducted before the COVID-19 pandemic and presents the risk factors before the pandemic which has become the focus of our lives and intense social media discourse. The effect of the COVID- 19 pandemic on the prevalence of VR for childhood vaccines and related factors has not been published yet. During the pandemic, childhood immunizations have been reported to be negatively affected due to the disruption to the delivery of vaccines globally rather than VR.[21-24] Bell et al.[25] have reported that most parents and guardians wanted to vaccinate their children during the pandemic although they experienced barriers that negatively affected their capability, motivation, and opportunity to vaccinate their children. Large population studies are necessary to evaluate the effects of the pandemic on VR rates regarding childhood vaccines.

When we evaluate the reasons from the participants' perspective, the most common reason to refuse the vaccines was the belief that they caused autism (63%), not surprisingly, but differing from the general population's perspective. Among them, 58% stated that they did not know 'which vaccine' and/or 'which component' might have caused. Furthermore, 92% of them stated that they did not know 'how?' vaccines caused autism. In the first report from our country about the intentions of childhood VR and hesitancy, Topçu et al.[26] reported that 12% of the participants stated that the reason for their refusal was the thought that vaccines caused autism. In a similar study evaluating the vaccine-related beliefs and practices among parents of children with ASD, Bazzano et al.[27] reported that the rate of the belief that vaccines caused autism was 48%. We believe

that evidence-based studies relating to ASD, their etiologic factors, and proven findings that vaccines are not associated with autism should be made public, and more readily available through social media as recently reported by Gabis et al.[28]

Parents generally complained that it was difficult to find unbiased and balanced information on both the expected benefits and possible side effects of vaccines, and health professionals are reported to be important sources of information on vaccines.[29] Our results support the literature that suggests that regular well-child visits with enough time and balanced information about the vaccines may prevent VR. According to our results, the lack of regular well-child visits increases the risk of developing VR in the study group.

A limitation of this study is that it is based on parental reports instead of medical records, thus cannot exclude recall bias although we believe VR was a deliberate decision among the participants. Another limitation is that some parents who did not accept to participate in this study could be VR cases, who did not want to face or discuss this with a doctor, thus, the rate of VR among ASD parents may be higher than we report. A strengthening point of this study is that it includes not only the opinions but also the attitudes on vaccines related to the following child's vaccination.

In conclusion, the prevalence of VR is increasing among parents of children with ASD and their immunization practices change for the consecutive child. High socioeconomic level, lack of regular well-child visits, and using social media as the main source of information increase the risk of developing VR in this susceptible population. Health professionals should be aware of this risk and evaluate the vaccination uptake of the younger siblings of children with ASD more carefully. The main points to prevent VR among parents of children with ASD are regular well-child visits, adequate immunization information, and improved media literacy.

Ethical approval

The study was reviewed and approved by the Local Ethics Committee of Behçet Uz Children's Hospital on 08.03.2018 (Protocol no: 2018/196, Decision No: 2018/05-01) and participation involved informed consent.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: ÖB, SAG; data collection: SAG; analysis and interpretation of results: SAG, ÖB; draft manuscript preparation: ÖB, SAG. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Prevalence of congenital hypothyroidism in North Macedonia: data from a newborn screening program conducted for twenty years

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ABSTRACT

Background. Congenital hypothyroidism (CH) is a common endocrine disorder that can be treated if timely detected by newborn screening, optimizing the developmental outcome in affected children. In the present study, we analyze the data of the national newborn thyroid screening program in North Macedonia collected over twenty years, including the CH prevalence as well as its geographical and ethnic variations.

Methods. The thyroid-stimulating hormone (TSH) was measured on a filter paper blood spot sample using the DELFIA fluoroimmunometric assay. A TSH value of 15 mIU/L whole blood was used as the cutoff point until 2010 and 10 mIU/L thereafter.

Results. Out of 377,508 screened live births, a total of 226 newborns with primary CH were detected, providing an overall prevalence of 6.0 per 10,000. Lowering the TSH cutoff led to an apparently increased prevalence of the transient CH, from 0.2 to 2.4 per 10,000 live births ($p<0.0001$) with an impact on the overall prevalence of primary CH (from 4.0 to 7.1 per 10,000, $p=0.0001$). Taking ethnicity into account, the significantly highest primary CH prevalence of 11.3 per 10,000 live births was observed among the Roma neonates, with a predominance of permanent CH (75.5%). There were also regional differences in the prevalence of primary CH. The highest primary CH prevalence of 11.7 per 10,000 live births was observed in the Vardar region, together with the highest regional prevalence of the transient CH (3.2 per 10,000). The highest prevalence of permanent CH was observed in the Pelagonia region (6.6 per 10,000) where the largest percentage of the Roma population lives.

Conclusions. The overall CH prevalence is high in North Macedonia, with substantial ethnic and geographical variations. Further analysis to elucidate the causes for the significant variations in the CH prevalence including environmental factors is warranted.

Key words: congenital hypothyroidism, ethnicity, prevalence, newborn screening, thyroid-stimulating hormone.

Congenital hypothyroidism (CH) is an endocrine disorder due to thyroid hormone deficiency present at birth, causing irreversible intellectual disability. It is classified as primary when the origin of the defect is in the gland itself, or secondary when the hypothalamic-pituitary axis is affected.[1-4] Primary CH can be further divided into permanent CH due to persistent thyroid hormone deficiency and transient CH that refers to a temporary deficiency of thyroid hormones.[1,5] Most neonates born with CH

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have a normal appearance without detectable physical signs, which can delay the diagnosis, leading to intellectual disability as the most severe outcome of the disease. Newborn thyroid screening allows early detection and treatment of CH so it is rightly considered one of the major achievements in preventive medicine that has changed the natural history of the disease and optimized the developmental outcome.[1,6] Additionally, the reported CH incidence of 1/7,000 to 1/10,000 prior to the onset of the newborn screening programs[7] was changed in the range between 1 in 2000-3000.[1,4] Different countries report different incidences of CH, and numerous studies are searching for the origin of these variations.[1-4]

The Republic of North Macedonia is a multiethnic country in the Balkan Peninsula with a population of approximately 2 million people.[8] It is divided into eight statistical regions (Eastern, Northeastern, Pelagonia, Polog, Skopje, Southeastern, Southwestern, and Vardar).[9] The newborn screening for congenital hypothyroidism in North Macedonia was introduced in April 2002 as a pilot study in five larger birth centers in the country. Since January 2007, it has become mandatory for all newborns in the country, as an integral part of the preventive programs for maternal and child health care of the Ministry of Health.

The aim of this retrospective study was to examine the national and regional CH prevalence in North Macedonia over the last two decades as well as the impact of the ethnic factor on the prevalence.

Material and Methods

Neonatal thyroid screening in North Macedonia is carried out by the centralized screening center located at the University Clinic for Pediatrics in Skopje, and covers a neonatal population of approximately 20,000 births per year. A total of 377,508 newborns delivered in all 27 public and private nurseries throughout the entire country were screened between April 2002 and April 2022. Whole blood was collected on filter paper Whatman 903 (Schleicher and Schuell Inc., Keene NH, USA) by neonatal heel prick, between 48 and 72 hours after birth. The whole-blood thyroid-stimulating hormone (TSH) was measured by the DELFIA time-resolved fluoroimmunometric assay based on the direct sandwich technique, in which two monoclonal antibodies (derived from mice) are directed against two separate antigenic determinants on the TSH molecule[10], using a neonatal TSH kit (DELFIA, Perkin-Elmer, Wallac Oy, Turku, Finland), and read by a 1420 VICTOR 2D Fluorometer (Wallac Oy, Turku, Finland). The analytical sensitivity of the DELFIA assays is typically better than 2 mIU/L blood. External controls from "Referenzinstitut fiir Bioanalytik," Bonn, Germany were included every 3 months. We have used a TSH cutoff value of 15 mIU/L whole blood until 2010 (period 1), and cutoff value of 10 mIU/L thereafter (period 2). The TSH values between 15 and 25 mIU/L in the period 1, and between 10 and 20 mIU/L in the period 2 were considered borderline and repeat analysis (new blood spot card) was requested usually 7 days after the previous test. The diagnosis of CH was made when the TSH level was higher than 10 mIU/L with low or normal thyroxine (T4) or free thyroxine (FT4) values on confirmatory serum measurements (IMMULITE 2000 chemiluminescent enzyme immunoassay system, Siemens Healthcare Diagnostics Inc., NY, USA). In all diagnosed children, treatment with L-T4 was immediately initiated.[11,12] The neonates with TSH serum levels between 5 and 9 mIU/L, and normal T4 level, were followed up every 15 days. Infants with repeatedly increased serum TSH levels (>5 mIU/L) up to 2-3 months of life also received substitution therapy with levothyroxine. The diagnosis of permanent vs. transient CH was made after a 4-weeks trial of treatment withdrawal in all children with "gland in situ" CH aged ≥3 years. The classification was made as follows: permanent CH (TSH>10mU/L, subnormal total or FT4), transient CH (normal thyroid tests after the trial off therapy and at least 6 months'follow-up period).[1,2] Based on this classification, only

CH cases obtained before 2020 (Apr 2002 – Dec 2019) were differentiated into transient and permanent forms of the disease, and used for assessing the prevalence of the transient and permanent CH while the remaining cases require more follow up, and those who were yet undetermined. This study was approved by the Ethical Committee of the University Clinic for Pediatrics, Faculty of Medicine in Skopje (Number: 12/2015 - 03-5515/13). The authors declare that all study procedures were in accordance with the Declaration of Helsinki and local laws and regulations. Formal consent was not required for the retrospective study.

Statistical analysis

Statistical descriptive analysis was performed using the Statistical Package for Social Sciences (version 20.0; SPSS Inc., Chicago, IL, USA). The comparison of two proportions was performed with Pearson χ^2 by MedCalc Software Ltd (Version 20.011, https://www.medcalc.org/calc/rate_comparison.php). Statistical significance was set at $p<0.05$.

Results

Over the twenty years of newborn thyroid screening, out of 388,940 live births, 377,508 have been screened. The nationwide coverage was 97.1%. It increased from 91.1% in 2002 to 98.8% in 2020. A total of 226 newborns with primary CH were detected with an overall prevalence of 1/1670 (6.0 per 10,000). Of them, 186 cases were differentiated into the permanent and transient forms of the disease. Thus, 135 (72.6%) of them had permanent CH and 51 (27.4%) were diagnosed with transient CH. In fact, a prevalence of 4 per 10,000 live births for permanent CH and 1.5 per 10,000 for transient cases ($p<0.0001$) was confirmed. Lowering the TSH cutoff from 15 to 10 mIU/L led to an apparently increased prevalence of the transient CH, from 0.2 to 2,4 per 10,000 live births ($p<0.0001$) while the prevalence of the permanent cases was insignificantly changed from 3.8 to 4.2 per 10,000 ($p=0.5864$). Moreover, the overall prevalence of primary CH was significantly increased (from 4.0 to 7.1 per 10,000 live births) after lowering the TSH cutoff value ($p=0.0001$).

Furthermore, we observed substantial regional variations of the primary CH prevalence (Table I). The highest CH prevalence of 11.7 per 10,000 live births was observed in the Vardar region, which was significantly different compared to the rates obtained in the Eastern region ($p<0.001$), Skopje ($p=0.003$), Southwestern ($p=0.005$) and Southeastern regions ($p=0.027$). In the Eastern region, the lowest CH prevalence in the country (2.1 per 10,000) was detected which was significantly lower than the rates observed in the Vardar region ($p<0.001$), Polog ($p=0.013$), Pelagonia ($p=0.002$), Skopje ($p=0.048$) and the Northeastern region ($p=0.027$). The evaluation of the prevalence of permanent CH in different regions showed the highest prevalence in the Pelagonia region (6.6 per 10,000) compared to the lowest prevalence of 1.8 per 10,000 live births detected in the Eastern region ($p=0.014$). On the other hand, the highest prevalence of the transient CH was detected in the Vardar region (3.2 per 10,000), while the lowest prevalence was observed in the Northeastern region (0.51 per 10,000), $p=0.070$.

We also found significant variations in the primary CH prevalence regarding the ethnicity. The highest primary CH prevalence of 11.3 per 10,000 live births was assessed among the Roma neonates with a predominance of the permanent CH (75.5%) in relation to the transient CH cases (23.5%), $p=0.031$. It was significantly higher in comparison with the primary CH rates obtained in all other ethnicities, Macedonian ($p=0.004$), Albanian ($p=0.012$) and Turkish ($p=0.001$), Table II. The lowest CH prevalence of 2.6 per 10,000 was detected among the Turkish neonates which was not statistically different from that in the Macedonian ($p=0.074$) and Albanian ($p=0.052$) neonates. Moreover, there was no statistically significant difference between detected the rates in the Macedonian and Albanian neonates, $p=0.633$ (Table II). The differentiation of the permanent CH cases from

Table I. Prevalence of primary CH in different regions of North Macedonia, during the period Apr 2002 - Apr 2022.

Region	Screened Newborns (n)	Newborns with Primary CH (n)	Incidence of Primary CH	CH Incidence per 10,000
Skopje	187,110	99	1/1890	5.3
Polog	42,989	30	1/1433	7.0
Pelagonia	43,376	37	1/1276	8.5
Eastern	18,812	4	1/4703	2.1
Northeastern	21,773	15	1/1452	6.9
Southwestern	24,910	10	1/2491	4.0
Southeastern	21,399	11	1/1945	5.1
Vardar	17,138	20	1/857	11.7
Total	377,508	226	1/1670	6.0

CH: congenital hypothyroidism, n: number of newborns with CH

Table II. Primary CH prevalence in North Macedonia by ethnicity, over twenty years (Apr 2002 - Apr 2022).

Ethnicity	Newborns with CH (n)	Incidence	Incidence per 10,000
Macedonians	113	1/1701	5.88
Albanians	82	1/1588	6.30
Roma	27	1/882	11.33
Turkish	4	1/3926	2.55

CH: congenital hypothyroidism

the transient ones in the Macedonian neonates did not show statistically significant differences (58.5% vs 41.5%, p=0.220) as well as in newborns of Albanian (48.8% vs 51.2%, p=0.878) and Turkish ethnicity (50% vs 50%).

Discussion

Newborn thyroid screening allows detection of CH shortly after birth in order to facilitate timely treatment and prevention of an irreversible neurodevelopmental delay optimizing its developmental outcome.[1,13,14] In 2007 after a five year pilot study it became mandatory in North Macedonia. The nationwide coverage over the two decades of the newborn thyroid screening program was 97.1%. An overall primary CH prevalence of 1/1670 live births was detected. It was higher than the last reported prevalence in the country (1/1976).[15] Lowering the TSH cutoff value from 15 to 10 mIU/L led to an almost two-fold increase in the primary CH prevalence (4 per 10,000 vs. 7.1 per 10,000). Similarly, a two-fold increase in the CH prevalence has been revealed by six newborn screening programs around the world, after lowering the TSH cutoff.[16] The increase in the prevalence of the primary CH is probably due to the 11-fold increase in the rates of transient CH cases detected after lowering the TSH cutoff value (p<0.0001), compared to the prevalence of the permanent CH (p=0.5864). The estimated prevalence of transient CH in the present study was 27% higher than previously reported in the country.[17] Lowering the TSH cutoff level contributed to the detection of transient CH cases in Central Serbia[18], Italy[19] as well as in Türkiye where an approximately 5-fold increase in transient CH prevalence (1/1154 vs. 1/6202) was reported.[20] In contrast, over a 37-year study period, prevalence of CH increased significantly in the Republic of Ireland despite a screening cutoff value that remained unchanged.[21] It is worth mentioning that lowering the neonatal screening TSH cutoff values, allows detection of newborns who would have been missed otherwise as

false negatives.[22] Furthermore, environmental, ethnic, and genetic factors should be considered in assessing the overall increase in CH prevalence.[23-25] For instance, some patients with the clinical expression of mutations in the *DUOX2*/*DUOXA2* genes required no treatment, and some of them had transient CH. On the other side, *DUOX* gene mutations can be associated with worsening of thyroid functions in the first weeks of life.[26] In a recent study that investigated genetic causes in Macedonian CH patients, *DUOX2* variants were identified in 5% of the "gland in situ" CH cohort (normal-sized, goitrous or hypoplastic thyroid glands). The heterozygous *DUOX2* variants were associated with transient hypothyroidism in all cases. However, monogenic *DUOX2* mutations are frequently associated with goitrous CH or TSH resistance.[27]

In the present study, we also revealed significant differences in the primary CH prevalence in neonates of different ethnic backgrounds. The primary CH prevalence in the Roma neonates (1/882) was almost two-fold higher than that among the Macedonians and Albanians, and 4-fold higher than that in the Turkish neonates. It was previously reported that high primary CH prevalence in one province of the Pelagonia region was associated with a higher percentage in the Roma population[28], as well as in the capital of the country[11] Similarly, the reported CH prevalence among Roma neonates (1/2192) in East Slovakia was statistically higher ($p<0.05$) than the one detected in white newborns (1/6284).[29] Genetic studies of the Roma population have shown high gene frequencies for private disease-causing founder mutations that often exceed the expected magnitudes for the global population. The limited gene flow points to the unique genetic heritage of the Roma, which makes this population genetically distinct from other European populations.[30] Furthermore, the predominance of permanent cases (75.5%) among Roma neonates with CH compared to other ethnicities could imply that genetic factors play a role in the ethnic variations of CH prevalence in the country.

In addition, we found the highest prevalence of permanent CH in the Pelagonia region (6.6 per 10,000), where the Roma population is the largest (3.4%), compared to the Southeastern region, which has only 0.4% Roma inhabitants ($p<0.0001$).[8,28] However, our results are in accordance with the reported data for the impact of the ethnic factor on the CH incidence.[24] Several US programs have obtained higher CH incidence in the Asian, Native American, and Hispanic populations and lower in the African American population.[2] Thus, race and ethnicity data revealed significantly higher CH incidence among Hispanic (6.1 per 10,000) and some Asian newborns (such as Asian Indians, 5.7 per 10,000) than among non-Hispanic white (3.6 per 10,000) and non-Hispanic black newborns (0.9 per 10,000) in California.[31] The processes of genetic drift and different levels and sources of admixture as well as the high fertility rate in the ethnic groups with a high risk for CH may have contributed to the rise of CH incidence.[32] Furthermore, the present study showed regional variations in the CH prevalence. The Vardar region had the highest primary CH prevalence which was 5-fold higher than the prevalence in the Eastern region, as a region with the lowest primary CH prevalence in the country. Taking into account that there is a similar ethnic composition in both regions with more than 80% of Macedonians, as a majority ethnic group[8,15], factors other than ethnicity are involved in different CH prevalence. Environmental factors such as exposure of chemical agents toxic to the thyroid gland may play a role in different regional variations in CH prevalence.[33] The natural and anthropogenic enrichment with heavy metals in the Vardar region, due to the location of two of the country's four smelter plants and the Allchar mine deposits on Kozhuf Mountain, may be linked to the highest prevalence of CH in this region.[15,34-36] However, more data are needed to elucidate this association. Moreover, we found the highest prevalence of the transient CH in the Vardar region (3.2 per 10,000), which was 6-fold higher in comparison with the lowest prevalence observed in the Northeastern

region (0.51 per 10,000), p=0.070. Given that iodine status is one reason for regional differences in CH prevalence, it is worth noting that the Republic of North Macedonia was designated an "iodine sufficient country" by the International Council for Control of Iodine Deficiency Disorders (ICCIDD) in 2018.[37,38] In Israel, however, there is a gradual decrease in CH incidence from the north to the south.[39] A recent study in China found that the prevalence of CH was significantly higher in coastal and inland areas than in remote areas, as a result of several suggested factors such as screening program practices, follow-up of screening positive cases, laboratory testing, and survival rates for preterm births across regions.[40] However, there is only one screening center in North Macedonia and all of the clinical centers that treat preterm births in the country are located in a single region (Skopje). Further analysis of the rate and proportion of the thyroid dysgenesis in different regions of the country is needed to assess the impact of the geographically delineated environmental exposure on the regional variations of the CH prevalence.

In conclusion, there has been a significant increase in the prevalence of primary CH in North Macedonia, probably due to an increased rate of transient CH cases after the lowering of the TSH cutoff value, as the most important factor. We found appreciable differences in the regional and ethnic-specific rates of CH over the two decades in North Macedonia. Further analysis to elucidate additional causes of the substantial variations in the CH prevalence is warranted since no complete data exist thus far.

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Ethical approval

The Local Ethics Committee and Human Research Ethics Committee of University Clinic for Pediatrics in Skopje, approved the study. (Number: 12/2015 - 03-5515/13).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: VA, MP, NZ, BZ, JMJ, MK; data collection: VA, MP, NZ; analysis and interpretation of results: VA, MP, NZ, MK; draft manuscript preparation: VA, BZ, JMJ. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

The risk factors for food allergy in infants with atopic dermatitis

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ABSTRACT

Background. There is a lack of information about which risk factors accompany food allergy (FA) in infants with atopic dermatitis (AD). We hypothesized that we would be able to predict FA through risk factors in infants with AD.

Methods. This prospective descriptive cross-sectional study was performed with infants aged 1-12 months with newly diagnosed AD. The SCORing Atopic Dermatitis (SCORAD) and Eczema Area and Severity Index (EASI), Infants' Dermatitis Quality Of Life (IDQOL), and Family Dermatological Life Quality (FDLQ) index scores were calculated at first admission. We developed a new tool, Sites of Eczema (SoE), to score sites of eczema on the body.

Results. A total of 279 infants with AD were included. FA was found in 166 (59.5%) infants with AD, of whom 112 had single and 54 had multiple FAs. The SCORAD index, EASI scores, IDQOL1, IDQOL2, and FDQL, and SoE scores were higher in the subgroup with FA compared to that without FA ($p<0.001$). In the multivariate regression model, eosinophil count (odds ratio [OR]=1.00, 95% confidence interval: [CI, 1.00-1.00]; p=0.008), serum total IgE level (OR=1.02, 95% CI: [1.00-1.03]; p=0.002), pruritus score (OR=0.87, 95% CI: [0.77-0.97]; p=0.019), SCORAD index (OR=1.04, 95% CI: [1.01-1.08]; p=0.008), FDQL index (OR=1.09, 95% CI: [1.01-1.18]; p=0.014), and SoE score (OR=1.48, 95% CI: [1.00-2.19]; p=0.046) were identified as the highest risk factors for FA in infants with AD.

Conclusions. Serum total IgE levels, eosinophil counts and ratio, SCORAD index and EASI scores, IDQOL and FDLQ index, pruritus and sleep disturbance scores, and SoE scores were identified as risk factors for FA in infants with AD in this study. The SoE score is an important risk factor for FA in infants with AD. We recommend that the risk factors for FA in patients with AD guide the management of these patients.

Key words: children, Eczema Area and Severity Index (EASI), Family Dermatological Life of Quality (FDLQ), Infants' Dermatitis Quality Of Life (IDQOL), SCORing Atopic Dermatitis (SCORAD), Sites of Eczema (SoE), total serum IgE.

Atopic dermatitis (AD) is the most common heterogeneous inflammatory skin disease, causing morbidity and a health burden in childhood. The prevalence of AD has increased in recent years up to an incidence of 15 to 20% among children. In addition to epidermal barrier dysfunction and immune dysregulation, other factors such as food allergy (FA) may also play a role in the etiopathogenesis of AD. FAs are seen more frequently in children with AD, as well as also being a factor that intensifies the severity and frequency of exacerbations of AD.[1-3]

AD management includes avoidance of individual trigger factors including food, using a moisturizer, and a step-up and step-down approach aimed at reducing inflammation according to the severity of the disease. The prevalence of FAs in patients with AD varies according to age and severity of AD. The

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prevalence of FAs is higher in infants with severe AD. FAs have been reported in 15% of children with mild-to-moderate AD. It has been reported that FA has been associated with children with moderate-severe and persistent AD in more than 50% of cases. Younger groups with AD are at a higher risk of FA.[4-6]

It is important to determine the diagnosis of FA, one of the obvious triggers for skin lesions and symptoms related to AD. Prompt and correct diagnosis of FA and food elimination will result in improvements in skin lesions, reduced drug use, and faster recovery times. It is not always easy to identify which infants have FA. AD and FA are often co-expressed, and the clinical manifestations of the two may overlap. The identification of possible factors that predict FA in infants with AD would be a useful guide in its management. There is also a lack of information in the literature about which risk factors accompany FA in infants with AD. In this study, we hypothesized that we would be able to predict FA through risk factors such as clinical findings, basic laboratory studies, and quality of life indices of infants with AD.

Material and Methods

Study design and population

This observational, descriptive, cross-sectional study was performed prospectively between January 2021 and February 2022. Parents of infants who presented to the Pediatric Allergy and Immunology Clinic as outpatients and who were newly diagnosed with AD were invited to participate in the study. We included the parents of infants aged 1-12 months who were selected to participate in this study based on the Hanifin-Rajka criteria.[7,8] Demographic features, skin prick test, serum total immunoglobulin (Ig)-E, specific IgE (SpIgE), and eosinophil count of patients were recorded.

The SCORing Atopic Dermatitis (SCORAD) index and Eczema Area and Severity Index (EASI) were calculated by the same physician (S.Ş.K.) at the first admission of the patients. In addition, Infants' Dermatitis Quality Of Life (IDQOL) and Family Dermatological Life of Quality (FDLQ) questionnaires were administered to the parents of the infants. Infants aged over 12 months, those diagnosed as having dermatosis, and infants with comorbidities such as primary immune deficiency were excluded. Infants whose parents were unable to understand the questions were also excluded.

The study was approved by the Ethics Committee of Dr. Sami Ulus Maternity and Children Training and Research Hospital (approval number: E-21/09-207).

Written informed consent was obtained from the parents for enrollment in the study.

Clinical scores

The clinical severity of eczema in infants with AD was evaluated using the SCORAD index and EASI.[9] The body surface area affected was calculated using the rule of nine for this index. SCORAD evaluates (1) the extent of the lesions, (2) the severity of the lesions with six clinical signs (erythema, edema/papulation, oozing/crust, excoriation, lichenification, xerosis), and (3) subjective items (including pruritus and sleep loss) using a visual analog scale (VAS). SCORAD has three sections - extent of illness, severity, and subjective symptoms, with a maximum possible score of 103. The severity of illness can be classified as mild (below 25 points), moderate (25-50 points), and severe (over 50 points) based on the SCORAD index.[10]

EASI is a tool used in the evaluation of four separate body regions (head/neck, trunk, upper and lower extremities) affected by erythema, induration/papulation/edema, excoriation, and lichenification. Each finding is scored between 0 and 3 according to the severity. The maximum possible EASI score is 72.[11]

The IDQOL questionnaire was administered to the parents. This contains 10 questions concerning symptoms and difficulties with mood, sleep (two questions), play, family activities, mealtimes, treatments, dressing, and

bathing. The maximum score for each question is 3, making a maximum possible score of 30. The higher the score, the greater the negative impact on the infant's quality of life. This questionnaire was identified as IDQOL1. There is an additional question that is scored separately, asking for the parents' own assessment of current dermatitis severity, giving a choice of four grades from none to extremely severe (0-4). These answers were identified as IDQOL2. This questionnaire has been validated in Turkish and is available on the official website of the university that conducted the questionnaire (www.cardiff.ac.uk).

The FDQL is used in the evaluation of the quality of life of parents of children affected by dermatologic diseases. The FDQL consists of 10 questions, each being scored between 0 and 3 depending on the severity (0 points none, 1 mild, 2 moderate, 3 severe). The maximum possible score is 30.[12] The Turkish language version of the FDLQ has been shown to exhibit high reliability and validity.[13]

The parents were asked to use a VAS to determine pruritus (range: 0-10) and sleep disturbance (range: 0-10).

Based on the eczema site, a simple new scoring was developed by modifying the EASI index for this study. The Sites of Eczema (SoE) system is a tool used in the evaluation each of four separate body regions (head/neck, trunk, upper and lower extremities). Each region was scored 1 point in the presence of eczema (Fig. 1).

Allergic assessment

The diagnosis of food allergy in AD is currently based on clinical history, skin prick tests (SPTs), or blood test screening, followed by an elimination diet and/or standardized oral food challenge (OFC). The presence of FA was confirmed in every child with a definite history of anaphylaxis and/or OFC.[14,15] Serum total IgE, food-specific IgE levels (Siemens Immulite 2000 CLIA-I, Germany), and eosinophil levels on peripheral smears (Beckman Coulter, Fullerton, CA, USA) were studied from blood samples.

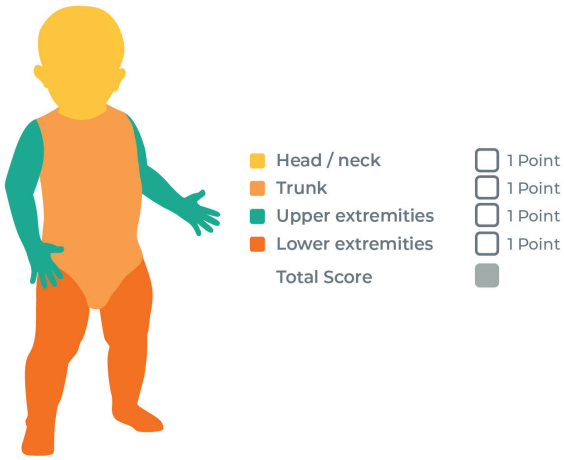

Fig. 1. Sites of eczema scores.

Sites of eczema (SoE) is a tool used in the evaluation of four separate body regions (head/neck, trunk, upper and lower extremities). Each region was scored 1 point in presence of eczema; the maximum score is 4.

SPTs were conducted with a panel including cow's milk, hen's egg, tree nuts, wheat, and soy (ALK-Abello, Madrid, Spain). Therewith, SPT was expanded individually to include each food suspected of allergy. Histamine (10 mg/mL) and saline were used as positive and negative controls, respectively. A positive SPT test was defined as a wheal with a mean diameter of at least 3 mm greater than that of the saline control.

Statistical analysis

Statistical analysis was performed using the SPSS version 26 software package. Categorical variables are shown as frequency and percentage values. The Kolmogorov–Smirnov test was used to determine whether the data conformed to normal distribution. Non-normally distributed numerical variables are presented as median and interquartile range. The chi-square and Fisher's exact tests were used to assess the differences between the frequency values. p values <0.05 were considered significant.

The sensitivity and specificity rates of the cut-off values of FA predictive factors in infants with AD were investigated using receiver operating characteristic (ROC) curve analysis. Youden's index was calculated to identify optimal cut-off points.

Factors emerging as statistically significant in the univariate binary logistic regression model were then evaluated in a multivariate binary logistic regression model. No clinically significant variable with a p-value between 0.25 and 0.05 for potential risk factors was found after univariate binary logistic regression. Due to the large number of variables, statistically non-significant (p>0.05) factors were excluded using the backward elimination method.

Results

A total of 279 infants with AD were included in this prospective, descriptive cross-sectional study (median age: 5 months, female/male ratio: 111/168). The median age of the infants was 5 months. One hundred seventy-nine (63.1%) of the infants were born via cesarean section delivery. Forty-eight percent of the infants had an allergic family history (mostly AD, followed by allergic rhinitis, asthma, urticaria, and drug allergy).

FAs were identified in 166 (59.5%) infants with AD, 112 of whom had single FAs and 54 had multiple FAs. The most common FAs were hen's egg, cow's milk, hazelnut, wheat, sesame, peanut, and walnut, respectively. The median eosinophil count was 450 count/mm^3, the percentage of eosinophils was 4.6%, and the median serum total IgE was 16.0 kU/L.

AD severity scores were measured. The median scores for pruritus and sleep disturbance were 7 and 4, respectively. The median SCORAD and EASI scores were 46 and 8, respectively. The median IDQOL1 and FDLQ scores were 10 and 12, respectively. The most frequent locations of eczema in infants with AD were the head/neck, trunk, the upper and lower extremities, in descending order.

The enrolled 279 infants with AD were further divided into two subgroups according to the presence of FA, 116 with FA and 113 without FA. Sex, age, delivery history, allergic family history, and type were compared, and the results were statistically similar between the subgroups (p>0.05).

When these two groups were further compared, eosinophil count and ratio, and serum total IgE levels were significantly higher in the subgroup with FA (p<0.001). Pruritus and sleep disturbance scores were also higher in the subgroup with FA (p<0.001 and p=0.023, respectively). The SCORAD index was higher in the subgroup with FA (median index 48 and 38, respectively; p<0.001). EASI scores were also higher in the subgroup with FA (median index 10 and 5, respectively; p<0.001). The quality of life of parents of children affected by AD was also evaluated according to the presence or absence of FA. IDQOL1 (median 11 and 8), IDQOL2 (median 3 and 2), and FDQL (median 14 and 9) scores in these FA subgroups were also measured, respectively (p<0.001).

When the FA subgroups were compared, even though the numbers of infants with eczema on the head/neck were the same, the numbers of lesions located on the trunk, and upper and lower extremities were higher in the FA-positive subgroup (p=0.016, p=0.001, and p=0.001, respectively). When the number of patients scoring 1 to 4 points on the SoE in the subgroups was compared, the number of patients scoring 2, 3, and 4 was higher in the FA-positive subgroup (p<0.001). The median SoE scores were higher in the subgroup with FA compared with the FA-negative subgroup (2 and 1, respectively; p<0.001). The demographic data and clinical features of the study groups and subgroup comparisons are shown in Table I.

Factors that predicted FA in infants with AD in the univariate regression model are shown in Table II: Serum total IgE, eosinophil count, eosinophil ratio, pruritus scores, sleep disturbance scores, SCORAD index, EASI scores, IDQOL1 index, IDQOL2 index, FDLQ index, and SoE scores, were identified as risk factors for FA in infants with AD. Age, sex, type of delivery, and familial history of allergy were not identified as risk factors for FA (p>0.05).

Factors that predicted FA in infants with AD in the multivariate regression model are shown

Table I. Demographic, laboratory findings, and clinical scores of all infants with AD and subgroups according to FA.

	Atopic dermatitis (overall) (n=279)	Food allergy (n=166)	No food allergy (n=113)	P value
Gender, n (%)				0.991
Female	111 (39.8)	66 (39.8)	45 (39.8)	
Male	168 (60.2)	100 (60.2)	68 (60.2)	
Age, months, median (IQR)	5 (3)	5 (2)	5 (3)	0.663**
Delivery, n (%)				0.348*
Caesarean	176 (63.1)	101 (60.8)	75 (66.4)	
Vaginal	103 (36.9)			
Allergic disease history in the family, n (%)	134 (48.0)	89 (53.6)	45 (39.8)	0.024*
Type of allergic disease history in the family (n=134), n (%)				0.394***
Atopic dermatitis	69 (51.5)	46 (51.7)	23 (51.1)	
Allergic rhinitis	35 (26.1)	2 (27.0)	11 (24.4)	
Asthma	15 (11.2)	9 (10.1)	6 (13.3)	
Urticaria	10 (7.5)	5 (5.6)	5 (11.1)	
Drug allergy	5 (3.7)	5 (5.6)	0	
Food allergy, n (%)				
Total of patients	166 (59.5)			
Single food allergy,	112 (40.1)	112 (67.5)		
Multiple food allergy, n (%)	54 (19.4)	54 (32.5)		
Type of food allergy, n (%)				
Hen's egg	151 (54.1)	151 (91.0)		
Cow's milk	45 (16.1)	45 (27.1)		
Hazelnut	12 (4.3)	12 (7.2)		
Wheat	8 (2.9)	8 (4.8)		
Sesame	8 (2.9)	8 (4.8)		
Peanut	7 (2.5)	7 (4.2)		
Walnut	6 (2.2)	6 (3.6)		
Eosinophil count (/mm^3), median (IQR)	450 (420)	555 (500)	390 (225)	<0.0001**
Eosinophil (%), median (IQR)	4.6 (3.5)	5.2 (3.8)	3.9 (2,4)	<0.0001**
Serum total IgE (IU/mL), median (IQR)	16.0 (23.2)	17.1 (32.8)	7.7 (12.8)	<0.0001**
Pruritus scores, median (IQR)	7 (3)	8 (2)	6 (4)	<0.0001**
Sleep disturbance scores, median (IQR)	4 (7)	4 (8)	2 (6)	0.023**
SCORAD scores, median (IQR)	46 (27)	48 (23)	38 (28.5)	<0.0001**
SCORAD index scores, n (%)				
Mild (<25)	35 (12.5)	4 (2.4)	31 (27.4)	
Moderate (25-50)	130 (46.6)	83 (50.0)	47 (41.6)	<0.0001*
Severe (>50)	114 (40.9)	79 (47.6)	35 (31.0)	
EASI scores, median (IQR)	8 (11)	10 (10.5)	5 (10)	<0.0001**
IDQOL1 scores, median (IQR)	10 (8)	11 (7.2)	8 (10.5)	<0.0001**
IDQOL2 scores, median (IQR)	3 (2)	3 (1)	2 (1)	<0.0001**
FDLQ scores, median (IQR)	12 (10)	14 (9)	9 (9)	<0.0001**
Sites of eczema, n (%)				
Head/neck	221 (79.2)	135 (81.3)	86 (76.1)	0.292*
Trunk	128 (45.9)	86 (51.8)	42 (37.2)	0.016*
Upper extremities	111 (39.8)	80 (48.2)	31 (27.4)	0.001*
Lower extremities	115 (41.2)	85 (51.2)	30 (26.5)	0.001*
SoE scores, n (%)				<0.0001*
1 point	98 (35.1)	33 (19.9)	65 (57.5)	
2 point	95 (34.1)	68 (41.0)	27 (23.9)	
3 point	56 (20.1)	42 (25.3)	14 (12.4)	
4 point	30 (10.8)	23 (13.9)	7 (6.2)	
SoE scores, median (IQR)	2 (1-4)	2 (1-4)	1 (1-4)	<0.0001**

*Chi-square test, **Mann Whitney U test, *** Fisher's exact test

EASI: eczema area and severity index, FA: food allergy, FDLQ: family dermatology life quality index IDQOL: infants' dermatitis quality of life index, IQR: interquartile range, SCORAD: severity scoring of atopic dermatitis, SoE: sites of eczema

Table II. Univariate regression model: the analysis of risk factors for food allergy in children with atopic dermatitis.

Risk factors	OR (95% CI)	p value
Gender	1.270 (0.771-2.093)	0.348
Age	1.079 (0.920-1.266)	0.348
Type of delivery	0.857 (0.409-1.796)	0.683
Familial history of allergy	1.051 (0.515-2.145)	0.891
Serum total IgE	1.029 (1.014-1.044)	<0.0001
Eosinophil count	1.002 (1.001-1.003)	<0.0001
Eosinophil (%)	1.209 (1.100-1.329)	<0.0001
Pruritus score	1.351 (1.201-1.520)	<0.0001
Sleep disturbance score	1.082 (1.010-1.158)	0.025
SCORAD index	1.044 (1.027-1.062)	<0.0001
EASI score	1.078 (1.040-1.118)	<0.0001
IDQOL1 score	1.101 (1.052-1.153)	<0.0001
IDQOL2 score	2.347 (1.722-3.199)	<0.0001
FDLQ score	1.151 (1.098-1.208)	<0.0001
SoE score	2.153 (1.614-2.872)	<0.0001

Cl: confidence interval, EASI: eczema area and severity index, FDLQ: family dermatology life quality index IDQOL: infants' dermatitis quality of life index, OR: odds ratio, SCORAD: severity scoring of atopic dermatitis, SoE: sites of eczema

Table III. Multivariate regression model: the analysis of risk factors for food allergy in children with atopic dermatitis.

Risk factors	OR (95% CI)	p value
Eosinophil count	1.001 (1.000-1.002)	0.008
Serum total IgE	1.021 (1.008-1.034)	0.002
Pruritus score	0.871 (0.777-0.978)	0.019
SCORAD index	1.049 (1.012-1.086)	0.008
EASI score	0.954 (0.888-1.005)	0.072
FDLQ score	1.098(1.019-1.183)	0.014
SoE score	1.487 (1.007-2.196)	0.046

Cl: confidence interval, EASI: eczema area and severity index, FDLQ: family dermatology life quality index IDQOL: infants' dermatitis quality of life index, OR: odds ratio, SCORAD: severity scoring of atopic dermatitis, SoE: sites of eczema

in Table III: Eosinophil counts, serum total IgE levels, pruritus scores, SCORAD index, FDQL index, and SoE scores were identified as the greatest risk factors for FA in infants with AD.

The ratios of the sensitivity and specificity of the cut-off values of FA predictive factors are shown in Table IV. The largest areas under the ROC curve (AUC) belonged to, in descending order, total IgE levels, FDQL scores, and SoE scores.

Discussion

This study evaluated the risk factors for FA in infants with AD. In the univariate regression model, serum total IgE levels, eosinophil counts, the eosinophil ratio, pruritus scores, sleep disturbance scores, SCORAD index, EASI scores, IDQOL1 index, IDQOL2 index, FDLQ index, and SoE scores were determined as risk factors in our study group. In the multivariate regression model, eosinophil count, serum total IgE levels, pruritus scores, the SCORAD index, FDQL index, SoE scores were associated with highest risk for FA in infants with AD. We suggest that if there is a presence of risk factors in infants with AD, detailed diagnostic tests should be performed to investigate FA.

AD is the most common heterogeneous inflammatory skin disease, with an incidence of 15 to 20% among children.[3] AD and FA are often co-expressed. FA has been reported in 15% of children with mild-moderate AD. FA has been associated with children with moderate-severe AD in more than 50% of cases. Infants with AD are at a particularly higher risk of FA.[4-6,16] This study represents an important guide for determining patients with FA in AD cases in infancy. AD requires long-term follow-up and care despite skin moisturizing, topical anti-inflammatory treatments, and nevertheless often does not heal completely. Infants with moderate-to-severe AD experience eczema, itching, and psychosocial problems.[17] Timely and accurate diagnosis of FAs is extremely important in these cases in clinical practice. The factors that facilitate the clinical decision of FA in terms of infant AD are presented in the present study.

Table IV. Cut-off values of predictive factors of food allergy and their sensitivity and specificity values in infants with atopic dermatitis.

Risk factors	Sensitivity (%)	Specificity (%)	AUC (95% CI)	p
Eosinophil count (/mm^3) >417	69.9	63.7	0.689 (0.626-0.752)	<0.0001
Serum total IgE (IU/mL) >13.1	71.1	63.7	0.732 (0.673-0.792)	<0.0001
Eosinophil (%) >4.3	66.9	60.2	0.670 (0.606-0.734)	<0.0001
SCORAD index > 44	63.9	58.4	0.680 (0.615-0.745)	<0.0001
IDQOL1 score >9	59.0	61.1	0.668 (0.600-0.736)	<0.0001
IDQOL2 score >2	78.9	53.1	0.686 (0.622-0.750)	<0.0001
FDLQ score>11	65.1	61.1	0.717 (0.654-0.779)	<0.0001
Sleep disturbance score >3	60.2	57.5	0.577 (0.509-0.646)	0.028
Pruritus score >6	64.5	66.4	0.678 (0.612-0.744)	<0.0001
EASI score >7	62.7	59.3	0.690 (0.624-0.756)	<0.0001
SoE score >1	80.1	57.5	0.698 (0.634-0.762)	<0.0001

AUC: area under the receiver operating characteristic (ROC) curve, CI: confidence interval, EASI: eczema area and severity index, FDLQ: family dermatology life quality index, IDQOL: infants' dermatitis quality of life index, OR: odds ratio, SCORAD: severity scoring of atopic dermatitis, SoE: sites of eczema

This study determined the cut-off values of risk factors that predicted FA in infants with AD. The sensitivity and specificity ratios of these factors may be a useful guide in clinical practice. In our study, Serum total IgE levels, FDLQ scores, and SoE scores were determined as the factors with the highest AUC values.

The prevalence of FA in children with AD is markedly higher than in children without eczema. The presence of eczema has been identified as one of the powerful risk factors for FA. In the HealthNuts cohort from Australia, the authors found that by 12 months of age, infants with eczema were 11 times more likely to develop peanut allergy and 5.8 times more likely to develop egg allergy, compared with infants without eczema.[18] We determined at least one FA in 59.5% of infants with AD in our study. The prevalence of FA is especially high in infants with moderate-severe AD. Most of our patients were infants with moderate and severe AD. Hen's egg (54.1%) and cow's milk FAs (16.1%) were the most frequent allergies. Other FAs detected included hazelnut, wheat, sesame, peanut, and walnut. Hen's egg and cow's milk have been observed most frequently in the literature.[18,19] We consider that the lower rate of peanut allergy in the present study than in the previous literature is due to the lower consumption of peanuts in Türkiye.

Several scoring systems have been developed to describe the clinical severity of AD. The SCORAD index is the most widely used and is frequently used in daily practice. The SCORAD index of infants with AD with FA was statistically significantly higher than those without FA in this study. Similarly, the number of infants with moderate-severe AD with FA was statistically significantly higher than those without FA. In a recently published article, the SCORAD index of infants with AD with FA was statistically significantly higher than that of those without FA, consistent with the present study. In addition, the prevalence of FA was higher in infants with moderate-severe AD than in those with mild AD.[17,20] EASI scoring is the second most frequently used system in children and adults, as recommended by Hanifin et al.[11] EASI scores were higher in infants with FAs in the present study.[21] The severity of eczema increases in patients with AD with FAs.

A new scoring system was employed in this study. SoE scores, a system designed for this study, were significantly higher in infants with AD with FA. Although there was no difference

between the subgroups with and without FA in terms of the presence of eczema in the head/neck region, infants with FA had significantly more eczema in the trunk, and upper and lower extremities. We determined that the presence of eczema in the head/neck region alone was not a risk factor for FA. In contrast, the risk of FA increases significantly in case of eczema in at least two regions. In the children with AD, eczema was common in areas that were exposed to the open air, including the cheeks and neck. Factors such as dry skin and irritation of the exposed areas lead to a disposition to eczema. However, in the presence of eczema on the trunk, legs, and arms, which are parts of the body less exposed to trauma, the risk of accompanying FA increases. We believe this will represent a practical clue to FA in infants with AD.[1,3]

The rate of cesarean birth and familial allergic disease history was significantly higher in infants with AD in the present study. Eosinophil counts and serum total IgE levels were significantly higher in the subgroup with FA. The pruritus and sleep loss scores evaluated according to the VAS were also higher in the subgroup with FA.

This study evaluated the IDQOL index, a quality of life score, and FDLQ, a family quality of life score, in infants with AD. Both scores were higher in infants with AD with FA compared with those without FA. The quality of life of the infant and parents was adversely affected in line with the clinical severity of eczema. Although family members of patients with dermatologic diseases experience many physical, social, and mental problems, this secondary effect is often neglected. Care and treatment costs impose extra burdens on family members, and emotional stress and social restriction may cause disruptions in family functioning. Additionally, family members may experience work-life problems due to the care and treatment of the patient. In addition to causing significant financial losses, this situation can lead to the deterioration of family harmony. The secondary effect on the family varies according to the diagnosis, duration, severity of the skin disease, the age of the patient, and especially depending on the relationships between the patients' family members. Healthcare providers should consider the magnitude of this secondary effect when presenting treatment plans and decisions to patients and families or conducting research.[22-24]

There are a number of limitations to this study. First, we observed an association between FA and the site of the eczema lesion in children with AD in clinical practice. We then established the SoE scoring system for the first time, and have provided a simple description of how this was applied in the present paper. We calculated SoE scores for our patients with AD. The data obtained were then presented as a preliminary scoring system. No comparison was performed with other scoring systems, for which reason validation with objective and more numerous data is required. Second, this study reveals that various factors are capable of predicting FA. However, the fact that the OR values of the risk factors identified in this study were statistically significant does not necessarily mean that they are important in clinical practice. However, further studies are now needed in order for these factors to guide the decision-making process in diagnosis and treatment management in children with AD in clinical practice.

In conclusion, FA has a negative effect that impacts the clinical severity and spread of eczema in infants with AD, as well as their quality of life. Early and accurate diagnosis of FA is very important in the follow-up of these patients. Serum total IgE levels, eosinophil counts and ratios, SCORAD index and EASI scores, IDQOL and FDLQ indexes, pruritus, and sleep disturbance scores were identified as risk factors for FA in infants with AD in this study. A new SoE score, a tool scored according to the sites of eczema on the body, was developed. SoE scores were found to constitute an important risk factor for FA in infants with AD. We consider that risk factors for FA in patients with AD will be a useful guide in the management of these patients.

Ethical approval

The study was approved by the Ethics Committee of Dr. Sami Ulus Maternity and Children Training and Research Hospital (approval number: E-21/09-207). Written informed consent was obtained from the parents for enrollment in the study.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: ZA, SŞK; data collection: ZA, SŞK; analysis and interpretation of results: ZA, SŞK, SÖ; draft manuscript preparation: ZA, SŞK, SÖ. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Primary ovarian tumors in children: a single center experience of 124 patients

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ABSTRACT

Background. Primary ovarian tumors are rare in the pediatric age group. We reviewed our 40-year experience with ovarian tumors to evalute the clinical features and treatment results in a single institution.

Methods. Between January 1975 and October 2015, 124 girls with primary ovarian tumor were diagnosed and treated in our center. Tumors were identified with biopsy or total resection and/or serum markers. Seventy four children were included in the treatment analysis.

Results. Median age for 124 children was 11.0 years (0.73-17.63). The main complaint was abdominal pain in 85 patients (68.5%). One hundred and five patients (84.6%) had total one-sided salpingo-oophorectomy and five patients had bilateral salpingo-oophorectomy. Amongst 124 cases, 29 patients had mature teratoma, which was the most common tumor in this study. Dysgerminoma (n=21) was the most common malignant histopathologic type. Stage I disease was diagnosed in 57.2% and stage IV in 6.6% of the patients. Five year overall survival (OS) and event-free survival (EFS) for 124 children were 82.5% and 76.3% respectively. For 74 children who received treatment, 5-year OS and EFS were 75.2% and 67.1%, respectively. Age ($p < 0.017$), histopathological subgroup ($p < 0.001$), stage ($p = 0.003$) and chemotherapy protocols ($p = 0.049$) were significant prognostic factors for OS.

Conclusions. The survival rates in children with ovarian tumors were comparable with studies in the literature. Although patients treated with platin based regimens had better survival rates, prognosis was still poor for the patients in advanced stages. This should be the focus for further studies and improvements.

Key words: childhood cancer, ovarian tumors, germ cell tumors.

Ovarian tumors are rare in the pediatric population and comprise approximately 1-2% of all childhood malignancies.[1-3] Limited information is available regarding the relative frequency of benign and malignant ovarian tumors in this age group. Ovarian tumors in childhood and adolescence include germ cell tumors (mature-immature teratoma, dysgerminoma, endodermal sinus tumor, embryonal carcinoma, choriocarcinoma, gonadoblastoma and mixed germ cell tumor), surface epithelial tumors (serous or mucinous cystadenoma, adenocarcinoma), sex cord–stromal tumors (Sertoli-Leydig cell tumors, granulosa cell tumors and gynandroblastoma) and miscellaneous tumors (malignant lymphoma and leukemia, small cell carcinoma, and soft-tissue tumors.[4] The most common types are germ cell tumors, both in benign and malignant groups.[5] Previous studies have predominantly focused on histopathologic subtypes and treatment protocols with small numbers of patients, most of these studies

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included germ cell tumors from other sites, apart from those of ovarian origin.[6-8] Although patients were treated with many regimens, an improvement in survival rate was accomplished only with the introduction of platin-based regimens.[6,8-10]

In this study, we report our experience with ovarian tumors in pediatric patients diagnosed at our institution between the years 1975 and 2015. We provide additional data regarding frequency, histological subtypes, clinical presentations and treatment results.

Material and Methods

Primary ovarian tumor was diagnosed in 124 patients between January 1975 and October 2015. All data used in this study were collected from institutional records. Initial symptoms, physical findings, surgical treatment, tumor histopathology, and staging was evaluated with The International Federation of Gynecology and Obstetrics (FIGO) and Children's Oncology Group (COG) treatment protocols and survival analyses were retrospectively evaluated.

Surgical methods included exploratory laparotomy and excision of the tumor with the ovary when possible. Surgeons also inspected the other ovary, abdominal organs, omentum, and lymph nodes and collected ascites or peritoneal washings for cytology when necessary.

Tumor staging was carried out according to the guidelines of FIGO and COG, as follows: COG, stage I was defined as a disease limited to ovaries; stage II as the tumor extended to the pelvis, stage III if intraperitoneal dissemination was noted, and stage IV if distant metastase was shown.[11,12] The FIGO staging system was revised in 2014.[13] We also evaluated the use of two different staging systems in pediatric ovarian tumors.

All surgical specimens were examined by the pathologist at the pediatric pathology department. Ovarian tumors were classified histologically according to the World Health Organization criteria.[14]

Serum alpha-feto protein (α-FP) and β-human chorionic gonadotropin (β-hCG) levels were measured and used as tumor markers in most of the patients. α-FP and β-hCG were not noted in files of patients diagnosed before 1984.

Patients with mature teratoma, who were treated in other centers or with stage I and II disease treated with surgery alone were excluded from the treatment analysis. Seventy-four children were analysed and all of them had been treated with chemotherapy regimens such as vincristine, adriamycin, cyclophosphamide (VAC), cisplatin, vinblastine and bleomycin (PVB) and bleomycin, etoposide and cisplatin (BEP) protocols. The VAC regimen was used from the years 1975 to 1986. Platin-based regimens such as PVB were used from the years 1986 to 1989 while BEP was used from 1989 onwards. Thus, three distinct time periods and treatment regimens were available for analysis. BEP regimen included bleomycin 15 units/m^2/day, IV, day 2; etoposide 100 mg/m^2/day, IV, days 1-3; cisplatin 100 mg/m^2/day, IV, day 1, every three weeks; PVB regimen consisted of cisplatin 120 mg/m^2/day, IV, day 1; vinblastine 0.15 mg/kg/day, IV, days 1–2 and bleomycin 10 mg/m^2/day, IV, days 2, 9, 16; VAC regimen had an induction of vincristine 2 mg/m^2/day, max 2 mg, IV, weekly for 12 weeks; dactinomycin 15γ/kg/day, IV, days 1-5; and cyclophosphamide 10 mg/kg/day, IV, days 1-3 and 20 mg/kg/day at weeks 3,6,9.; and maintenance for every 4 weeks, vincristine 2 mg/m^2/day, max 2 mg, IV, days 1 -5; dactinomycin 15γ/kg/day, IV, days 1-5; and cyclophosphamide 10 mg/kg/day, IV, days 1-3, every 4 weeks. AVAC had adriamycin 30 mg/m^2/day, days 1-2, IV, instead of dactinomycin in the VAC regimen. The patients were evaluated after three cycles of therapy, and fourteen with residual disease underwent surgery. Those with malignant disease in resected specimen received at least three or more additional cycles of their assigned regimen.

Radiotherapy was administered to 24 patients. Five patients received radiotherapy as the first line of treatment after surgery before the year 1980 (three with dysgerminoma, one with embryonal carcinoma and one with malignant teratoma). After the year 2000, radiotherapy was used only in two patients, one with mixed germ cell tumor and the other with immature teratoma with disseminated and recurrent disease respectively.

Mean and median values were used for analysing demographic characteristics. Events and survival estimates were obtained using the Kaplan-Meier method. Differences in survival curves were tested using the log-rank test.[15]

The study was approved by Hacettepe University Ethical Board (number: 2020/13-07).

Results

Clinical characteristics

One hundred and twenty four patients with a primary ovarian tumor between the years 1975 and 2015 were analyzed. The median age of patients at the time of diagnosis was 11.0 years (range 0.73-17.63) with only one patient being younger than 12 months. Most ovarian tumors were seen in the age group of 10 to 14 years (58 patients, 46.7%). However, in the whole group, malignant ovarian tumors were seen more frequently in children under five years of age. The presenting symptoms (Table I) were predominantly abdominal pain (85 patients, 68.5%), 60 patients (48.5%) had both abdominal pain and distension. Three patients had no symptoms at all; of these, two were diagnosed during routine clinical checkup and follow-up for mixed gonadal dysgenesis and spinal muscular atrophy type 3, respectively. One patient had an ovarian tumor without symptoms and was incidentally diagnosed. In the eight girls, acute abdominal pain was noted, 4 of whom underwent emergency surgery for the presumed diagnosis of ovarian torsion. An abdominal mass was found in 87 patients (70.2%) during physical examination.

Table I. Symptoms at diagnosis of 124 pediatric patients with ovarian tumors.

	N	%
Abdominal pain	85	68.5
Abdominal swelling	60	48.5
Abdominal pain and swelling	27	21.7
Nausea and womiting	13	10.4
Anorexia and weakness	8	6.4
Menstrual irregularities	8	6.4
Fever	4	3.2
Urinary complaint	4	3.2
Constipation	3	2.4
Puberte precox	3	2.4
Dyspnea	3	2.4
No symptoms*	3	2.4
Other**	1	0.8

* One patient had mixed gonadal dysgenesis, one had spinal muscular atrophy, the other patient was diagnosed during a check-up.
** A patient had growth delay, and developmental intellectual disability.

Lag time is defined as the duration between the onset of symptoms and establishment of a definitive diagnosis. Thirty two patients were diagnosed on the first day of onset of symptoms while the longest lag time was one year for a patient with intermittent abdominal pain. The median lag time was 20.5 days (1-365 days). The patients (n=29) with mature teratoma had a median lag time of ten days (1-150 days). The lag time for patients (n=21) with dysgerminom a was 15 days (1-180 days).

Disease location

Sixty-six patients (53.2 %) had right, 51 (41.2%) had left ovarian involvement and 6 (4.8%) had bilateral involvement. Laterality could not be identified in one patient.

Surgical details

Of the 124 patients, 105 had unilateral and 5 had bilateral salpingooopherectomy. Eleven underwent tru-cut biopsy at admission, while one was diagnosed by inguinal lymph node biyopsy. Two patients were diagnosed with tumor markers alone and did not undergo surgery.

Table II. Distribution of COG and FIGO staging system in 124 children with ovarian tumors.

	COG staging				
FIGO staging	Stage I	Stage II	Stage III	Stage IV	Total
Stage I	69	1	0	0	70
Stage II	2	11	5	0	18
Stage III	0	1	27	1	29
Stage IV	0	0	0	7	7
Total	71	13	32	8	124

COG: Children's Oncology Group, FIGO: International Federation of Gynecology and Obstetrics

A unilateral salpingo-oophorectomy was performed in 105 patients. Seventy nine patients had neither macroscopic nor microscopic disease; fourteen patients had microscopic disease. Twelve patients had partial resection with gross residual disease. Five patients underwent surgery for bilateral salpingo-oophorectomy (3 of whom had no microscopic disease). Eleven patients had biopsy only; five of them were diagnosed with laparotomy (either tru-cut or laparotomy). Fourten patients had a second look surgery.

Staging

The staging was performed according to the FIGO system and resulted in the following distribution: Stage I disease was found in 56.5% of the patients; stage II in 14.5%, stage III in 23.4%, and stage IV in 5.6% patients. Stage distribution according to the COG staging system, identified stage I disease in 57.2% of the patients, stage II in 10.4%, stage III in 25.8%, and stage IV in 6.6% of the patients. There were only ten patients who had different stages according to both staging systems (Table II).

Histopathologic Findings

Of the 124 ovarian tumor specimens examined, 29 (23.4%) were mature teratoma and this was the most common tumor type in our study. Hispathological distribution is shown in Table III. Dysgerminoma was the most common malignant histopathologic type (n=21, 16.9%) followed by the mixed germ cell tumor, which accounted for 13.7% (n=17). Other tumor types identified included unclassified germ cell tumors (n=4), granulosa cell tumors (n=4), adenocarcinoma (n=1), and gonadoblastoma (n=2). We also had one patient with a cystadenoma, two patients with Sertoli-Leydig cell tumors and one patient with a borderline mucinous tumor. *DICER1* mutation was not investigated in Sertoli-Leydig cell tumors.

Tumor Markers

Tumor markers α-FP and β-hCG were unavailable and not measured in patients diagnosed before the year 1984. We found high α-FP levels in 46 patients and high β-hCG

Table III. Histopathogical distribution of 124 pediatric patients with ovarian tumors.

Histopathological distribution	N	%
Germ cell tumors		
Mature teratoma	29	23.4
Dysgerminoma	21	16.9
Mixed germ cell tumor	17	13.8
Endodermal sinus tumor	14	11.3
Embryonal carcinoma	13	10.5
Immature teratoma	12	9.7
Teratocarcinoma	2	1.6
Malignant teratoma	1	0.8
Unclassified germ cell tumor	4	3.2
Epithelial tumors		
Adenocarcinoma	1	0.8
Mucinous tumor	1	0.8
Serous cystadenoma	1	0.8
Sex cord stromal tumors		
Granulosa cell tumor	4	3.2
Gonadoblastoma	2	1.6
Sertoli-Leydig cell tumor	2	1.6
Total	124	100

levels in 25 patients. The highest β-hCG level (285.500 mIU/ml) was found in a patient with unclassified germ cell tumor and this patient had an α-FP level of 1300 ng/ml. She did not undergo surgery or a biopsy but was instead diagnosed based on tumor marker levels. Additionally, there was another patient who was diagnosed only based on tumor marker levels without a biopsy or surgery. High serum α-FP level at diagnosis was not a significiant factor for 5-year overall survival (OS) and event-free survival (EFS) (patients with normal vs high level of α-FP; OS 79.3% vs 72.4%, p=0.84; EFS 75.9% vs 61.2%, p=0.26).

Chemotherapeutic regimens

Several chemotherapeutic regimens were used in our center during the study years based on the year of diagnosis. Seventy-four patients were treated with chemotherapy in this study. Patients who received chemotherapy at other centers before referral were excluded from the analyses. Forty-eight cases (64.9%) were treated with the BEP (bleomycin, etoposide, cisplatin) regimen, 14 (18.9%) with PVB regimen, 12 (16.2%) with VAC and AVAC (only one patient with adriamycin plus VAC).

Radiotherapy

Twenty-four patients received radiotherapy for disease progression, disseminated abdominal diseases and recurence. Five patients received radiotherapy as the first line treatment after surgery before the year 1980, three had dysgerminoma, one with embryonal carcinoma and one with malignant teratoma.

Survival analysis

We performed survival analysis using data from 74 patients who received chemotherapy. The OS at five years in all 74 patients was 75.2% while the EFS rate was 67.1% (Fig. 1). The OS was significiantly different among different age groups (p=0.017) (Fig. 2). Patients treated with the BEP protocol had the best survival rates. The OS and EFS rates for the VAC regimen

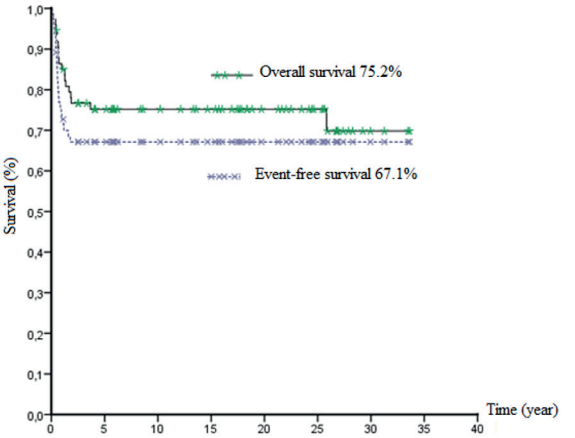

Fig. 1. Overall and event-free survival of 74 patients with malignant ovarian tumors (The numbers show the five year survival rates).

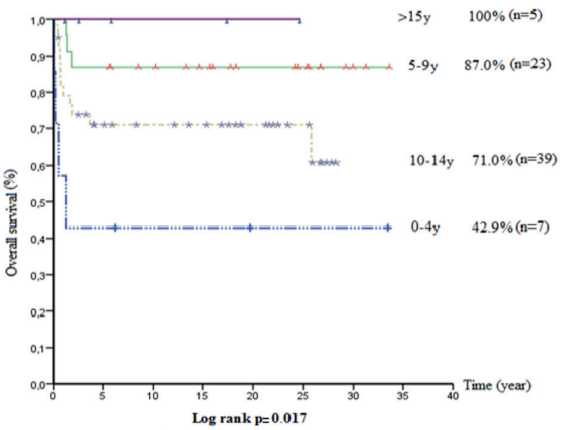

Fig. 2. Overall survival of children with malignant ovarian tumors according to age groups (The numbers show the five year survival rates).

at five years were 66.7% and 50%, 57.1% and 42.9% for PVB, and 82.5 % and 78.5% for BEP, respectively (Fig. 3 and 4). Survival rates according to the chemotherapy regimens were significantly different (p =0.049). Other factors that were significantly associated with overall survival were age (p <0.017), histopathological subgroup (p <0.001), FIGO stage (p =0.019) and COG stage (p =0.003) (Table IV). Since the germ cell tumors were the major group of ovarian tumors in this study, we conducted a detailed survival analysis for 113 germ cell tumors. The overall and event-free five-year survival rates of 113 patients diagnosed with germ cell tumors were 82.9% and 76.2% respectively.

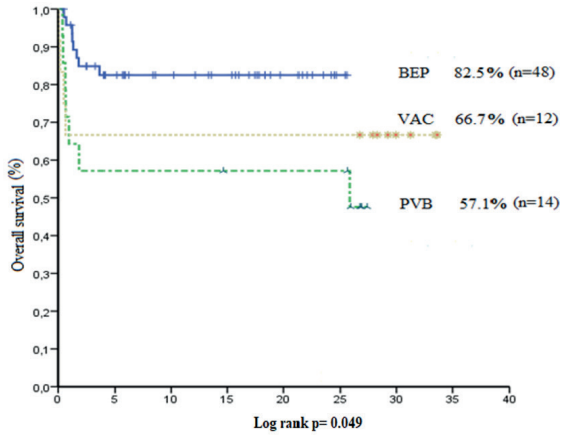

Fig. 3. Overall survival according to treatment regimens for malignant ovarian tumors of children (The numbers show the five year survival rates).

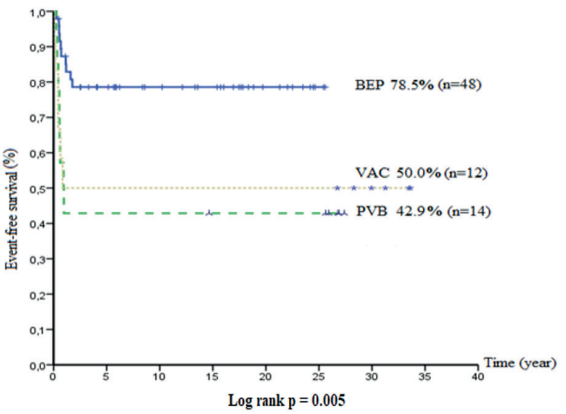

Fig. 4. Event-free survival according to treatment regimens for malignant ovarian tumors of children (The numbers show the five year survival rates).

Table IV. Overall and EFS rates according to the histopathological types and stages in 74 patients receiving chemotherapy regimens.

			Survival rates for five years (%)	
	N	%	OS	EFS
Histopathological subgroups				
Dysgerminoma	18	24.3	83.3	77.8
Mixed germ cell tumor	17	22.9	75.3	63.0
Endodermal sinus tumor	13	17.5	67.1	67.1
Embryonal carcinoma	12	16.2	75.0	50.0
Immature teratoma	7	9.5	71.4	71.4
Teratocarcinoma	2	2.7	50.0	50.0
Malignant teratoma	1	1.4	-	-
Unclassified germ cell tumor	4	5.4	100	100
COG				
Stage I	25	33.7	95.8	91.8
Stage II	13	17.6	84.6	69.2
Stage III	29	39.1	58.6	48.3
Stage IV	7	9.6	45.7	45
FIGO				
Stage I	24	32.4	95.7	95.7
Stage II	18	24.3	72.2	55.6
Stage III	26	35.1	65.4	53.8
Stage IV	6	8.1	31.3	31.3

OS rates for COG staging p= 0.003, EFS rates for COG staging p= 0.008, OS rates for FIGO staging p= 0.019, EFS rates for FIGO staging p= 0.005, OS rates for histopathological subgrup p< 0.001, EFS rates for histopathological subgrup p< 0.001

COG: Children's Oncology Group, EFS: event-free survival, FIGO: International Federation of Gynecology and Obstetrics, OS: overall survival

Five-year OS and EFS were 100 % & 100% for mature teratoma, 85.7% and 81% for dysgerminoma, 75.3% and 63% for mixed germ cell tumors, 69.6% and 70.1% for endodermal sinus tumors, 76.9% and 53.8% for embryonal carcinomas, and 81.8% and 71.4% for immature teratomas.

Discussion

This retrospective study aimed to analyse the different ovarian tumors, regarding the clinical features, parameters affecting prognosis, assess the long-term follow-up of children with malignant ovarian tumors and compare data with other published studies in the literature. There are several studies on the ovarian tumor in children in the literature.[5,8,16-25]

124 cases with ovarian tumors were represented in this series, in which 91.1% were germ cell tumors, 2.4% were epithelial tumors and 4.8% were sex-cord stromal tumors. Seventy-five percent of all ovarian tumors and 74.3% of germ cell tumors were malignant in our study. Bhattacharyya et al. published a series of 151 girls with ovarian tumors aged 0-20 years, in which 38% of the patients had germ cell tumors.[22] In the same study, 66% of germ cell tumors were malignant and dysgerminomas were the most common malignant tumor. Breen et al. reported that 35% of all ovarian neoplasms in children and adolescents were malignant.[3] The rate of malignant ovarian tumors in our study was higher than others because most patients were referred to our hospital after a malignant disease diagnosis had been obtained.[19,26-29]

In our study, the most common ovarian tumor was the mature teratoma (23.4%) and the most common malignant germ cell tumor was dysgerminoma. Similar results have been previously reported.[30-33] The proper distinction of malignant and benign cases are critically important for the management of ovarian tumors. The main presenting complaints were abdominal pain followed by distention. Presentation with acute abdomen was a frequent occurrence and was noted in 6.4% of the patients. Baranzelli et al. stated that 11% of the girls with ovarian tumor had acute abdominal pain.[34] Sixty-six patients (53.2%) had a tumor on the right ovary and 51 (41.1%) had a tumor on the left ovary and 6 (4.8%) had bilateral involvement. One patient's primary tumor could not be detected by radiologic scanning. The frequencies of dysgerminoma, mixed germ cell tumor, immature teratoma, and endodermal sinus tumor were similar to that reported in the literature.[30-35]

In our study, the OS and EFS were significiantly different among the various histopathologic subgroups ($p < 0.001$). Patients with dysgerminoma, immature teratoma, and endodermal sinus tumor survived longer compared with other tumor types. Ablin et al. reported that histopathologic subgroups among malignant germ cell tumors was not associated with the outcome.[20] Other studies were not able to definitively address this subject.[36-38] This needs to be investigated in prospective studies.

Secretion of α-FP and less commonly β-hCG can be important for diagnosis, assessing treatment response and post-treatment surveillance.[39] In our study, the primary tumor was not detected in one patient and she was instead diagnosed based on tumor markers. Other patients who had high α-FP levels during the follow-up period had relapses. Thus, we suggest to evaluate tumor markers in all ovarian germ cell tumors for diagnosis and during follow up and relapse. The Children's Cancer and Leukaemia Group, the French Society of Pediatric Oncology and the COG have previously identified serum α-FP as a prognostic factor.[23,40] Murugaesu et al. mentioned that pre-treatment tumor markers levels are valuable for predicting recurrence and OS.[41] Tangjitgamol et al.[42] stated that only perioperatif tumor markers significantly affects the progression-free survival. The survival rates were lower in patients with high α-FP levels but not statistically signficant in our study.

Standard management of ovarian tumors is surgical removal which allows a definitive histopathological diagnosis and subsequent chemotherapy.[43-45] The tumor should be removed as much as possible.[46] In our study, a total resection without microscopic residue was performed in ninety three patients (75.1%) at diagnosis. We think that second-look surgery should only be performed in patients who had any residual masses after three or four courses of chemotherapy. Eight patients had no active tumor at second-look surgery, but one of them relapsed during follow-up period. There are no conclusive reports in the literature to recommend the need for second-look surgery; most of the studies had a small sample size.[43-45]

Although all ovarian masses in girls most commonly occur between the ages of 15 and 19 years, ovarian cancer is rarely seen under the age of ten.[16,47,48] In our study, 58 (46.8%) of 124 patients were diagnosed in the ages between 10-14 years and 40 (32.3%) were in the ages of 5-9 years. The median age was 11.0 years (0.73-17.63). We even had a patient under the age of one in this series. 74 patients who received chemotherapy regimens were analysed for survival rates according to the age groups. The OS rate of patients over the age of 15 years was 100%, while that of patients in the 0-4 year group was 42.9%. We also found a relationship between age and disease progression in our study (p= 0.017). Poorer prognosis was found in younger patients. While, contrarily earlier studies reported that age did not have a significiant influence on survival, last studies showed that age is an important risk factor for progression and survival.[49,50] This should be investigated in further studies.

FIGO and COG were used for staging in this study. We suggested that COG staging is more useful for the retropective studies because FIGO staging system requires detailed information of the operation and cytopathological evaluation. Both systems are effective for staging in pediatric tumors. For practical reasons, the COG system is easy to learn and implement in centers which do not have a high patient volume.

Survival in patients with lower stages have better survival rates. For treatment analysis of 74 patients, the best survival was found in patients who had stage I tumors according to both systems of classification as expected. Overall survival rates of stage I disease for COG and FIGO was 95.8% and 95.7%, respectively (p= 0.003 / p= 0.019). Survival results of COG were 84.6%, 58.6%, 45.7% for stage II, III and IV, respectively. According to FIGO systems, survival rates were 72.2%, 65.4%, 31.3% for stage II, III and IV, respectively. Ablin et al. mentioned that metastases of the germ cell tumors did not affect the prognosis.[20] But we observed that advanced disease with metastasis had poorer prognosis in our study. Wollner et al. reported that 32 patients diagnosed with germ cell tumors had EFS rates of 100% for stage I, 80% for stage III, and 67% for stage IV.[36] Lockley et al.'s review of ovarian cancer in adolescense and young adults suggested that the patients diagnosed with an ovarian germ cell tumor had better survival rates (<90%) than other epitelial ovarian tumors.[51] Marina et al. also showed that patients with low-grade ovarian tumors had a better survival rate than advanced stage diseases and that 5 year EFS rates for 137 patients were 84.8% in those with stage III disease and 78% in those with stage IV tumors.[37] In the study by Billmire et al., the patients (n=25) underwent initial surgery for stage I malignant germ cell tumors and 5 year OS rate was 96% after three cycles of BEP with an EFS rate of 52%.[24] The SFOP (Societe Francaise d'Oncologie Pediatrique) study from France which included 12 girls with stage I ovarian tumors there were six relapses; five of them received successful salvage chemotherapy and one patient died due to non-responsiveness.[34] Rogers et al. showed that patients below 21 years of age with stage I and stage II ovarian malignant germ cell tumors had 6 year OS rates of 95% and 93.8%, respectively.[7] In the CCSG (Children's Cancer Study Group) study from the United Kingdom which included nine girls with stage I ovarian tumors who were treated with surgery only, three cases had relapse and all of them underwent successful salvage chemotherapy.[40]

The COG/CCG group presented 124 cases with ovarian germ cell tumors and compared survival rates after three vs four cycles of BEP regimen. The EFS rates were 88% vs 92%, respectively.[52] In our study, survival rates in the early stages of the disease are similar to the published results but survival rates in the advanced stages are lower based on the different time periods of our center. The survival rates need to be improved in these cases.

Three different chemotherapy regimens were used in our center during the years 1975-2015. The best results were seen with the BEP protocols. Overall survival rate for five years in BEP regimen was 82.5%. The patients who received PVB and VAC had OS rates for five years as 57.1% and 66.7% respectively (p = 0.049). For five years, EFS rates were 78.5%, 42.9% ve 50.0% for BEP, PVB and VAC regimens, respectively (p= 0.005). Kapoor et al. reported OS after five years to be 83% with the BEP protocol in patients with germ cell tumors.[53] In a review, Gershenson suggested that the BEP protocol is superior to VAC and PVB protocols in the management of the ovarian tumor.[46] Ghosn et al. recommended high dose cisplatin, ifosfamide and etoposid in refractory germ cell tumors, but the response rate was relatively low and the regimen had high toxicity rates.[54] The COG pilot study regarding escalating doses of cyclophosphamide did not have better responses than standard BEP regimens.[55] The COG/CCG group study showed that the frequency of treatment-related toxicity increased in children with testicular and ovarian tumors receiving BEP regimen with high-dose cisplatin (40 mg/m2/day, 1-5 day) versus low dose cisplatin (20mg/m2/day, 1-5 days).[6] Survival rates for BEP regimen is similar to the literature and we suggest that the BEP regimen is an appropriate and effective regimen for pediatric ovarian tumors.

Currently the main treatment is surgery and chemotherapy but, in the past, the standard of care also included adjuvant abdominal radiotherapy. It's known that germ cell tumors especially, dysgerminoma and embryonal carcinoma are very radiosensitive.[56] However, radiotherapy is no longer standard practice in chilldren, largely due to high toxicity rates and the effectiveness of platinum-based chemotherapy for ovarian tumors.

In conclusion, the BEP regimen remains the best option while high risk patients should be treated with more intensive treatment strategies.

The level of care in pediatric oncology in Türkiye is getting better. As an upper middle income country, we have to focus to improve survival rates in advanced cases. Professional awareness, structured referral systems and investment in strengthening the health system will help to improve survival rates to the level of high income countries.

Ethical approval

The study has been approved by Hacettepe University Ethical Board (number: 2020/13-07).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: MC, TK, AV; data collection: MC, TK; analysis and interpretation of results: MC, TK, AV; draft manuscript preparation: MC, TK, AV, BY, BA, NK, CA. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Clinical characteristics of patients requiring lung transplantation referral in national cystic fibrosis registry data

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ABSTRACT

Background. We aimed to determine the number of cystic fibrosis (CF) patients recorded in the Cystic Fibrosis Registry of Türkiye (CFRT) who were in need of lung transplantation (LT) referral and examine clinical differences between patients who were LT candidates due to rapid forced expiratory volume in one second (FEV_1) decline and LT candidates without rapid FEV_1 decline in the last year to identify a preventable cause in patients with such rapid FEV_1 decline.

Methods. All CF patients recorded in the CFRT in 2018 were evaluated in terms of LT. Patients were divided into those with FEV_1 below 50% and in need of LT due to a decrease of 20% or more in the previous year (Group 1) and those who did not have FEV_1 decline of more than 20% in the previous year but had other indications for LT (Group 2). Demographic and clinical features were compared between the two groups.

Results. Of 1488 patients registered in CFRT, 58 had a need for LT. Twenty patients were included in Group 1 and others in Group 2. Our findings did not reveal any significant variations in treatment, chronic infection status, or complications between the two groups. The average weight z-score was significantly higher in Group 1. Positive correlations were detected between weight z-score and FEV_1 in 2017 in Group 1 and between FEV_1 values in 2017 and 2018 in Group 2.

Conclusions. There appears to be a relationship between the nutritional status and weight z-scores of CF patients and pulmonary function, which may indirectly affect the need for lung transplantation referral.

Key words: cystic fibrosis, lung transplantation, registry.

Cystic fibrosis (CF) is an autosomal recessive disease affecting approximately 1 in 2500 to 3500 newborns.[1,2] Lung disease remains the primary cause of morbidity, and end-stage lung disease remains the primary cause of mortality in CF patients. Lung transplantation (LT) has recently become the standard care[3,4], as it not only provides an additional management option but can also improve quality of life and survival.[5] However, finding a suitable transplant can take a long time. Moreover, LT is a major operation that may have serious complications and requires substantial amounts of medication postoperatively.[6] The most common indications for LT are interstitial lung diseases, advanced chronic obstructive pulmonary disease, cystic fibrosis, emphysema due to alpha-1-antityripsin deficiency, pulmonary arterial hypertension and re-transplantation in adults, while it is CF, idiopathic pulmonary arterial hypertension, and interstitial lung diseases among children.[7,8]

The pulmonary component of CF is characterized by progressive airway inflammation and recurrent lower respiratory infections that cause bronchiectasis and chronic respiratory failure, leading to significant morbidity and mortality in this population.[9] Nevertheless, a multidisciplinary approach and the introduction of modulators that directly target the basic defects in CF have improved patients' quality of life and life expectancy, which is now more than 40 years.[10]

A total of 2514 pediatric lung, 733 pediatric heart-lung, 69 200 adult lung, and 4128 adult heart-lung transplantations performed worldwide had been recorded in the International Thoracic Organ Transplant Registry by June 30, 2018.[7,11] While the annual pediatric LT number has remained stable, the number of heart-lung transplantations is decreasing.[7] CF is the most common indication for LT in children over the age of 11 years, accounting for 65%, compared to 48% in ages 6 to 10 years. In ages 1 to 5 years, the percentage of LT for CF is 3.4%.[6] In adults, it is the third most common indication in patients with advanced CF lung disease.[12] In the Thoracic Organ Transplant Registry, the total LT rate for adult patients with CF reported in 2019 was 15.2%, and most cases were bilateral (97.6%).[11]

In this study, we aimed to compare clinical features of patients with CF with an indication for LT referral with a rapid decrease in forced expiratory volume in the first second (FEV_1) in the last year and patients with other LT indications.

Material and Methods

Data of patients who were recorded in the Cystic Fibrosis Registry of Türkiye (CFRT) in 2018 and performed pulmonary function tests (PFT) were evaluated. CF patients who met the LT referral criteria according to the current guidelines[3] were included the study (Box 1). The patients were divided into those who had an FEV_1 % of under 50% and a decline of more than 20% in the previous year (Group 1) and those who did not have a rapid FEV_1 decline but had other indications for LT seen in Table 1 (Group 2). The flow chart of the study population is given in Fig. 1.

The patients' demographic and clinical characteristics were recorded, and comparisons between the two groups were performed. The analyzed characteristics included age, age at diagnosis, gender, first and second sweat chloride test results, weight and height z-scores, body mass index (BMI) in 2018, genetic mutations, FEV_1% values in 2017 and 2018, death, treatments, chronic infection status, complications, and history of meconium ileus. The z-scores were calculated as the ratio of the difference between the observed measurement and the sample mean to the standard deviation of the sample to describe how many standard deviations height and weight were above or below the sample mean. For patients under 18 years old, malnutrition was defined as having a BMI below the 5th percentile, and for patients 18 years or older, malnutrition was defined as having a BMI below 18.[3] Genetic mutations were classified as severe if two mutations were class I, II, or III and mild if one or more mutations were class IV or V.[13,14] Treatments included inhaled hypertonic saline, inhaled mannitol, inhaled antibiotics, bronchodilators, recombinant

Box 1. Lung transplantation criteria (adapted from Cystic Fibrosis Foundation Consensus Guideline[3]).

For individuals with CF who are under the age of 18 years old should be referred for LT when;

- FEV_1 is under 50% predicted and rapidly declining (>20% relative decline in FEV_1 within 12 months) or
- FEV_1 below 50% with markers of shortening survival;
  - room air hypoxemia (SpO_2 < 88% or PaO_2< 55mmHg at rest or with exercise, at sea level),
  - hypercarbia ($PaCO_2$ >50mmHg confirmed on arterial blood gas),
  - 6 minute-walking-test (6MWT) distance under 400 meters or
  - pulmonary hypertension findings (such as pulmonary arterial systolic pressure above 50 mmHg on echocardiogram or evidence of right ventricular dysfunction in the absence of a tricuspid regurgitant jet)

or

  - body mass index (BMI) under 5 percentile
- FEV_1 is below 40% predicted.

For individuals with CF who are 18 years and older, the CF Foundation recommends LT referral when;

- FEV_1 is under 50% predicted and rapidly decreasing (>20% relative reduction in FEV_1 in the last 12 months) or
- FEV_1 is below 40% predicted with markers of shortening survival;
  - BMI < 18 kg/m^2 or
  - scrambling to improve the nutritional status
  - more than two pulmonary exacerbation per year requiring intravenous antibiotics or 1 exacerbation requiring positive pressure ventilation (PPV) regardless of FEV_1 or
  - massive hemoptysis requiring intensive care unit (ICU) admission or
  - bronchial artery embolization or
  - pneumothorax or
  - regardless of FEV_1 when 6MWT distance under 400 meters or
  - hypoxemia or
  - hypercarbia or
  - pulmonary hypertension occurs) or
- FEV_1 is < 30% predicted.
- For females and individuals with short stature (height <162 cm) the CF Foundation also recommends special consideration for LT.

Table I. Clinical features of the entire study population.

Clinical feature	n	%
Gender (male/female)	29/29	50/50
Age <18 years	33	56.9
Age ≥18 years	25	43.1
History of meconium ileus	2	3.4
Treatment with		
Inhaled hypertonic saline	16	27.6
Inhaled mannitol	17	29.3
Inhaled antibiotic	40	68.9
Bronchodilator	30	51.7
rhDNase	58	100
Inhaled steroid	17	29.3
Oral steroid	4	6.9
Azithromycin prophylaxis	15	25.8
Ursodeoxycholic acid	15	25.8
PERT	55	94.8
PPI	16	27.6
Oxygen	15	25.8
NIPPV	11	18.9
Chronic infection status		
Pseudomonas aeruginosa	45	77.6
Staphylococcus aureus	25	43.1
Burkolderia cepacia	2	3.4
Haemophilus influenzae	7	12
Nontuberculous mycobacteria	1	1.7
Stenotrophomonas maltophilia	6	10.3
Achromobacter	4	6.9
MRSA	9	15.5
Complication related to CF		
Osteoporosis	13	22.4
Liver disease	9	15.5
ABPA	6	10.3
Hemoptysis	2	3.4
Clinical features	Mean ± SD	
Age (years)	18.8 ± 7.5	
Age at diagnosis (years)	5.2 ± 8.5	
Weight z-score	−1.8 ± 0.7	
Height z-score	−1.7 ± 1.3	
Body mass index	15.5 ± 3.0	
Body mass index z-score	−1.4 ± 0.7	
First sweat chloride test value (mmol/L)	96.9 ± 25.3	
Second sweat chloride test value (mmol/L)	96.1 ± 24.9	
FEV_1 value in 2017 (%)	48.4 ± 21.1	
FEV_1 value in 2018 (%)	32.9 ± 8.6	

ABPA: allergic bronchopulmonary aspergillosis, CF: cystic fibrosis, FEV1: forced expiratory volume in the first second, MRSA: methicillin-resistant *Staphylococcus aureus*, NIPPV: noninvasive positive pressure ventilation, rhDNase: recombinant human DNase, PERT: pancreatic enzyme replacement treatment, PPI: proton pump inhibitor, SD: standard deviation.

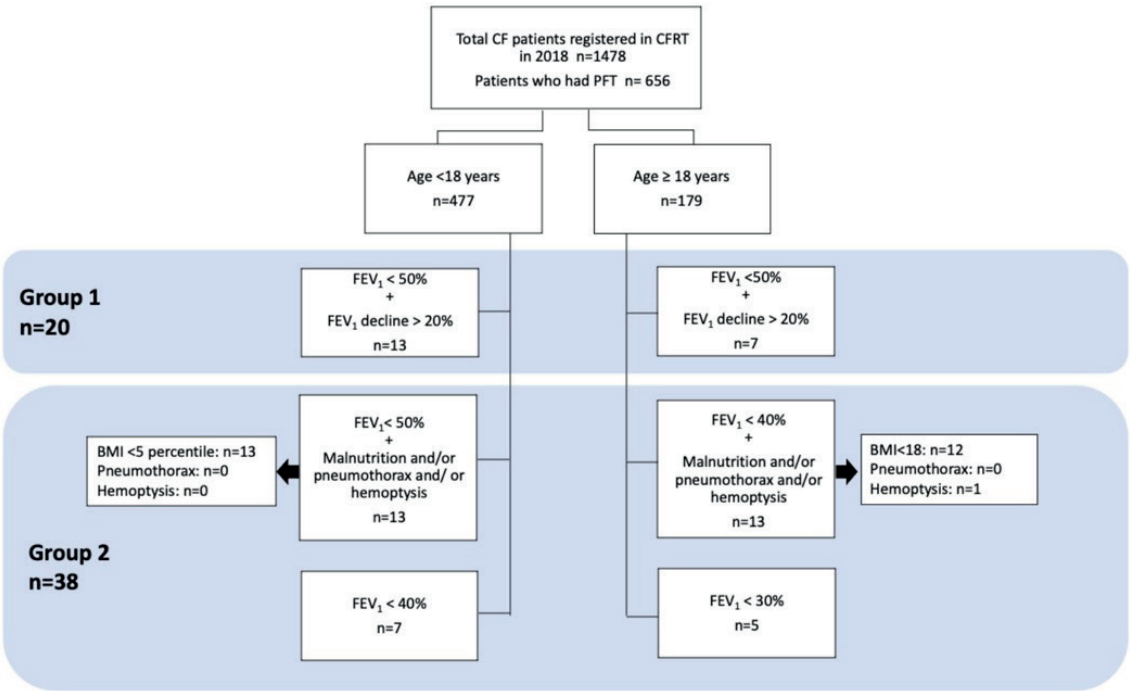

Fig. 1. The flow chart of the study.

human DNase (rhDNase), inhaled/oral steroids, azithromycin prophylaxis, ursodeoxycholic acid, pancreatic enzyme replacement treatment (PERT), proton pump inhibitors, and oxygen or noninvasive positive pressure ventilation (NIPPV). Chronic infection status was defined as three samples taken consecutively from the respiratory tract in the previous six months with at least one-month intervals[15] testing positive for *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Burkholderia cepacia*, *Haemophilus influenzae*, nontuberculous mycobacteria, *Stenotrophomonas maltophilia*, *Achromobacter*, or methicillin-resistant *Staphylococcus aureus* (MRSA). Complications included allergic bronchopulmonary aspergillosis (ABPA), distal intestinal obstruction syndrome (DIOS), hemoptysis, pneumothorax, osteoporosis, liver disease, CF-related diabetes mellitus, and pseudo-Bartter syndrome.

Statistical analysis

IBM SPSS Statistics 22.0 (IBM, Armonk, NY, USA) was used for the statistical analysis. For descriptive statistics, categorical variables were expressed as numbers and percentages, and continuous variables were expressed as means ± standard deviations or medians and ranges. To assess the statistical significance of numerical differences, independent sample t-test was used when the assumption of normal distribution was satisfied for the sample, and Mann-Whitney U test was used when the assumption was not satisfied. For comparisons between the two groups, Pearson chi-square test was used to assess the statistical significance of categorical differences. The relationship between data that did not conform to a normal distribution was evaluated by Spearman's correlation test, and the data that fit the normal distribution was evaluated by Pearson's correlation test. A p-value of less than 0.05 was considered statistically significant.

The study was conducted in accordance with the ethical standards of the institutional and/or national research committee (Hacettepe University Ethics Board, date: 12 April 2007, reference number: HEK 07/16-21 and date: 5 June 2018, reference number: GO 18/473-31) and with the 1964 declaration and its later

amendments or comparable ethical standards. Informed consent was obtained from all patients or their parents/ legal guardians.

Results

A total of 1488 CF patients were recorded in the CFRT in 2018, 656 of whom had PFT results. Of those, 58 (3.9%) met the LT criteria according to the current guidelines.[3] Twenty-nine patients (50%) were male. Thirty-three (56.9%) patients were under 18 years old. The median age of the patients was 17 years (range: 8.0–44.5 years), and the median age at diagnosis was 0.7 years (range: 0.1–41.0 years). The mean FEV_1 was 48.4% ± 21.1% in 2017 and 32.9% ± 8.6% in 2018. The average weight z-score was −1.8 ± 0.7, the average height z-score was −1.7 ± 1.3, and the average BMI z-score was −1.4 ± 0.7. All patients were receiving rhDNase, about one third of patients were receiving inhaled hypertonic saline, inhaled mannitol, and most of them were receiving PERT. Chronic infection with *P. aeruginosa* was the most common whereas nontuberculous mycobacteria was the least. The most common complication related to CF was osteoporosis. None of the patients included in the study had DIOS, pseudo-Bartter syndrome, pneumothorax, or CF-related diabetes or malignancy in 2018 and until 2018, 2 patients with CF who were registered in CFRT underwent LT. The clinical features of the entire study population are shown in Table I.

A total of 20 (34.5%) patients, 13 of whom were under 18 years of age and 7 were aged 18 and above, had FEV_1 under 50% and a decline of more than 20% in the previous year (Group 1). A total of 38 (65.5%) patients did not have a rapid FEV_1 decline in the previous year but had other indications for LT (Group 2). Thirteen of them were under 18 years old and had FEV_1 under 50% and a weight z-score below −2 and/ or pneumothorax and/or hemoptysis. Seven patients were aged under 18 and had FEV_1 under 40%. Thirteen patients were aged 18 and above and had FEV_1 under 40% and BMI below 18 and/or pneumothorax and/or hemoptysis. Five patients were aged 18 and above and had FEV_1 under 30%.

The median age of the patients was 16.6 years (range: 8–44.5 years) in Group 1 and 17.8 years (range: 10.1–41.9 years) in Group 2. The difference was not statistically significant (p = 0.659). The median age at diagnosis was 0.6 years (range: 0.1–41) years in Group 1 and 2 years (range: 0.1–37 years) in Group 2 (p = 0.302). More than half of the patients in Group 1 and about half of the patients in Group 2 were males (p = 0.581). Out of a total of 20 patients in Group 1, 13 (65%) were under the age of 18 years, compared to 20 out of 38 patients (52.6%) in Group 2 (p=0.126). There were no significant differences in the first and second sweat chloride test results between the two groups (p = 0.813 and p = 1.000, respectively). The average weight z-score was significantly higher in Group 1 than in Group 2 (−1.4 ± 0.8 and −2.0 ± 0.7, respectively; p = 0.011). Likewise, the mean BMI z-score was significantly higher in Group 1 than in Group 2 (−1.01 ± 0.86 and −1.57 ± 0.59, respectively; p = 0.015). The median height z-scores, on the other hand, did not differ significantly between Groups 1 and 2 (−1.7 [range: −3.4 to 1.4] and −2.1 [range: −4.2 to 1.8], respectively; p = 0.141). In Group 1, 35% (7 out of 20 patients) were found to be malnourished, while in Group 2, 73.6% (28 out of 38 patients) had malnutrition (p=0.001). Two (10%) patients in Group 1 and no patients in Group 2 had a history of meconium ileus. Because of the insufficient number of patients, a statistical analysis could not be performed.

Five (25%) patients in Group 1 and five (13.1%) in Group 2 had a heterozygous F508del mutation. Four (20%) patients in Group 1 and nine (23.6%) patients in Group 2 had a homozygous F508del mutation. The differences between the two groups were not statistically significant (p = 0.748 and p = 0.512, respectively). In total, 13 (65%) patients in Group 1 and 19 (50%) patients in Group 2 had severe genetic mutations, with no statistically significant difference between the two groups (p = 1.000). The FEV_1 values in 2017 and 2018 did not differ significantly between the two groups (p = 0.366 and

p = 0.255, respectively). No patients in Group 1 died during 2018, whereas five patients (13.2%) in Group 2 died during the same period. The demographic and clinical characteristics of the patients in Groups 1 and 2 are displayed in Table II.

In terms of treatments, one third of patients in Group 1 and one fourth of patients in Group 2 were receiving inhaled hypertonic saline (p = 0.392). About half of the patients in Group 1 and one fifth of patients in Group 2 were receiving inhaled mannitol (p = 0.057). More than half of the patients in Group 1 and more than three fourth of patients in Group 2 were receiving inhaled antibiotics (p = 0.095). One fifth of the patients in Group 1 and more than one fourth of patients in Group 2 were receiving oxygen (p = 0.460), while one fifth of patients in Group 1 and about one fifth of patients in Group 2 were receiving NIPPV (p = 1.000). The treatments in the two groups are shown in Table III.

Chronic infection with *P. aeruginosa* was the most prevalent, whereas infection with nontuberculous bacteria was the rarest. There were no statistically significant differences between the two groups in terms of chronic infections. The chronic infection status of the patients in the two groups is displayed in Table IV.

Osteoporosis was the most common complication, whereas DIOS, pseudo-Bartter syndrome, pneumothorax, and CF-related diabetes or malignancy were not noted.

In terms of FEV_1, a positive correlation was observed between FEV_1 in 2017 and the weight z-score in Group 1 (r = 0.521, p = 0.018). In Group 2, a positive correlation was found between the FEV_1 value in 2018 and that in 2017 (r = 0.768, p = 0.004) (Table V).

Table II. Comparison of demographic and clinical characteristics of patients with rapid FEV_1 decline and patients with other indications for lung transplantation.

Demographic and clinical characteristics	Group 1 n= 20	Group 2 n= 38	p
Age (years), median (range)	16.6 (8-44.5)	17.8 (10.1-41.9)	0.659[a]
Patients under the age 18, n (%)	13 (65)	20 (52.6)	0.126[b]
Age at diagnosis (years), median (range)	0.6 (0.1-41)	2 (0.1-37)	0.302[a]
Gender (male), n (%)	11 (55)	18 (47.4)	0.581[b]
FEV_1 in 2017 (%), mean ± SD	59.4 ± 18.6	30.2 ± 9.1	0.366[c]
FEV_1 in 2018 (%), mean ± SD	34.5 ± 10.2	32.5 ± 9.4	0.255[c]
First sweat chloride test value (mmol/L), mean ± SD	95.5 ± 28.2	92.3 ± 25.1	0.813[c]
Second sweat chloride test value (mmol/L), median (range)	96 (71-127)	96 (63-170)	1.000[a]
Weight z-score, mean ± SD	−1.4 ± 0.8	−2.0 ± 0.7	**0.011[c]**
Height z-score, median (range)	−1.7 (−3.4 to 1.4)	−2.1 (−4.2 to 1.8)	0.141[a]
Body mass index, mean ± SD	16.6 ± 3.3	14.9 ± 2.7	0.061[c]
Body mass index z-score, mean ± SD	−1.01 ± 0.86	−1.57 ± 0.59	**0.015[c]**
Presence of malnutrition, n (%)	7 (35)	28 (73.6)	**0.001[b]**
Genetic mutation, n (severe/mild)	13/1	19/3	1.000[b]
Heterozygous F508del mutation, n (%)	5 (25)	5 (13.1)	0.748[b]
Homozygous F508del mutation, n (%)	4 (20)	9 (23.6)	0.512[b]

FEV_1: forced expiratory volume in the first second, SD: standard deviation
[a] Mann-Whitney U test
[b] Chi-square test
[c] Independent sample t-test
P-values less than 0.05 were considered statistically significant and marked in bold.

Table III. Treatments in Groups 1 and 2.

Treatment	Group 1 n (%)	Group 2 n (%)	p
Inhaled hypertonic saline	7 (35)	9 (24.3)	0.392[a]
Inhaled mannitol	9 (45)	8 (21.1)	0.057[a]
Inhaled antibiotic	11 (55)	29 (76.3)	0.095[a]
Bronchodilator	9 (45)	21 (55.3)	0.457[a]
rhDNase	20 (100)	38 (100)	
Inhaled steroid	7 (35)	10 (26.3)	0.490[a]
Oral steroid	0 (0)	4 (10.5)	
Azithromycin prophylaxis	4 (20)	11 (28.9)	0.460[a]
Ursodeoxycholic acid	5 (25)	10 (26.3)	0.913[a]
PERT	19 (95)	36 (94.7)	1.000[a]
PPI	4 (20)	12 (31.6)	0.348[a]
Oxygen	4 (20)	11 (28.9)	0.460[a]
NIPPV	4 (20)	7 (18.4)	1.000[a]

NIPPV: noninvasive positive pressure ventilation, PERT: pancreatic enzyme replacement treatment, PPI: proton pump inhibitor, rhDNase: recombinant human DNase
[a] Chi-square test

Table IV. Chronic infection status of patients in Groups 1 and 2.

Chronic infection	Group 1 n (%)	Group 2 n (%)	p
Pseudomonas aeruginosa	14 (70)	31 (81.6)	0.339[a]
Staphylococcus aureus	8 (40)	17 (44.7)	0.729[a]
Burkholderia cepacia	0 (0)	2 (5.3)	
Haemophilus influenzae	5 (33.3)	2 (10)	0.112[a]
Nontuberculous mycobacteria	0 (0)	1 (2.6)	
Stenotrophomonas maltophilia	4 (20)	2 (5.3)	0.168[a]
Achromobacter	2 (13.3)	2 (10)	1.000[a]
MRSA	3 (20)	6 (31.6)	0.697[a]

MRSA: methicillin-resistant *Staphylococcus aureus*
[a] Chi-square test

Table V. Relationship between FEV_1 values and weight, height and BMI z-scores over two consecutive years.

			FEV_1 in 2017	FEV_1 in 2018	Weight z-score	Height z-score	BMI z-score
Group 1	FEV_1 in 2017	p	1	0.233	0.018	0.351	0.069
		r		0.279	0.521	-0.220	0.415
	FEV_1 in 2018	p	0.233	1	0.684	0.129	0.717
		r	0.279		-0.097	-0.351	-0.086
Group 2	FEV_1 in 2017	p	1	0.004	0.768	0.482	0.974
		r		0.768	0.095	-0.225	0.011
	FEV_1 in 2018	p	0.004	1	0.443	0.103	0.333
		r	0.768		-0.128	-0.269	-0.161

BMI: body mass index, FEV_1: forced expiratory volume in the first second

Discussion

This registry-based study aimed to compare the clinical characteristics of CF patients who needed LT referral due to a rapid decline in FEV_1 and who did not exhibit a rapid decline in FEV_1 but had other indications for LT referral by using the data of CFRT. We found that according to the latest guidelines, 3.9% of CF patients in Türkiye registered in CFRT were in need of LT referral. In our study, more than half of the patients in need for LT were in the pediatric age group. In total 20 patients had rapid decline on FEV_1 in the last year and became candidates for LT. When the demographic and clinical characteristics of the patients were compared, the weight z-score and BMI z-scores were found to be higher in patients with FEV_1 decline more than 20% in the last year than others. So, a rapid FEV_1 decline in the previous year was found to be associated with the patients' nutritional status and weight z-scores. There were no significant differences in chronic infection status, treatments, or complication status between patients with and without a rapid decline in FEV_1. This may be because both groups in the study had advanced lung disease and were candidates for lung transplantation, even though for different reasons.

Over the years, the rate of adult CF patients who have been followed-up has increased. Consequently, LT is seen more frequently in adults. An estimated 8% of CF patients undergoing LT in Canada from 1988 to 2016 were pediatric patients.[9] In the Italian CF registry, 8 (10.8%) of 76 CF patients undergoing LT in 2015 and 2016 were in the pediatric age group.[16] In the 2017 annual report of the European Cystic Fibrosis Society (ECFS), 32 (10.7%) of 299 patients undergoing LT were in the pediatric age group.[17] Since the number of LT in Türkiye is low, the patients who are candidates for LT were reviewed and 56.9% of the patients who were recorded in the CFRT and needed LT according to the latest guidelines were found to be in the pediatric age group.[3] This may be because the CFRT started recently, and more than half of registered patients are under 18 years of age. Moreover, adult patients' follow-up is not yet at the desired level. Over time, more adult CF patients are expected to be followed up closely.

Malnutrition and low BMI are associated with poorer pulmonary outcomes and are significant predictors of poor survival and earlier progression toward the need for LT in CF.[18,19] Because high basal metabolic rates with both exocrine and endocrine dysfunction predispose CF patients to undernutrition and low weight; their nutritional status should be closely monitored during long-term follow-ups.[19] On the other hand, it is also possible that severe lung disease itself may be associated with a poor nutritional state due to increased energy needs, decreased appetite, and gastrointestinal involvement, such as reflux and nausea.[20] Kerem et al.[20] found that a low BMI was the strongest potentially preventable factor for severe lung disease in patients recorded in the ECFS Patient Registry. Poor pulmonary function was six times higher in severely undernourished patients than in patients with normal BMI.[20] In our study, BMI average values and height z-scores were similar in patients with rapid FEV_1 decline and patients with other indications. Patients in Group 2 had a higher rate of malnutrition due to its inclusion criteria. Moreover, the weight and BMI z-scores were significantly lower in patients who had other indications for LT other than rapid FEV_1 decline. This may be because, apart from a rapid FEV_1 decline, patients can be candidates for LT due to poor nutritional status. It is also known that pancreatic insufficiency in CF patients doubles the risk of severe lung disease.[19] Monitoring and improving CF patients' nutritional status is a cornerstone of management to slow the progression to end-stage lung disease.[19] It is important to note that the presence of other conditions, such as pulmonary hypertension and right heart failure, in patients with advanced lung disease can negatively impact their nutritional status.[21] It is important to consider the potential adverse effects of poor nutritional status on the progression of lung

disease and the development of comorbidities, as these factors may further exacerbate the nutritional status and overall clinical condition of the patient. As our study highlights, it is important to remember that there are numerous factors, in addition to nutritional status, that can affect the candidacy of patients with advanced lung disease and CF for LT.

Because of CF patients' variable course of disease, the prediction of prognosis is often difficult. Milla and Warwick[22] found that the rate of yearly FEV_1 decline is a better predictor of early mortality than the FEV_1 percentage alone. As a result of our study, we would like to emphasize that the long-term follow-up of the nutritional status besides the lung functions of patients with CF is more important than the changes in the last 1 year. It should be kept in mind that CF patients should be followed up closely with a multidisciplinary approach, especially in terms of pathogen colonization, malnutrition, and complications that may affect lung function.

Although we included all CF patients recorded in the CFRT, our study has some limitations. One of them was the small sample size of the population included the study. This may undermine some differences between the two groups. Unfortunately, we were unable to include several important variables in the analysis, including hypercarbia, hypoxemia, six-minute walk-test results, pulmonary hypertension, number of hospitalizations, pulmonary exacerbations, and frequency of antibiotic use. Additionally, we were unable to include information about whether or not the patients were receiving adequate nutrition and dietary support or the timeframe in which this was provided because these data were not recorded in the CFRT. Also, the reason why there is a significant difference in the weight z-score and the BMI between the two groups is because low BMI could be a criterion for being included in Group 2 but not in Group 1. Additionally, it was also noteworthy that the mean FEV_1 values of the patients in Group 2 were higher in 2018 than in 2017. The fact that the expected decrease in FEV_1 was not seen in this group over the past year may be due to the intensive regulation of the treatment of the patient group who already have low FEV_1 values.

Patients with CF may develop end-stage lung disease in the long term for various reasons and become candidates for LT. As the number of patients recorded in the CFRT increases, the registry will provide clinicians with more information and assist in the identification of patients in need for LT. All CF patients' nutritional status should be carefully monitored. Weight gain is essential for CF patients to avoid the need for LT. Early identification of poor nutritional status could prevent lung function deterioration and delay the progression to end-stage lung disease. A yearly FEV_1 decline of 20% or more may not be associated with other clinical parameters. Overall, our findings highlight the importance of long-term monitoring of CF patients' clinical and nutritional status to protect lung functions and to identify patients in need of LT referral.

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Ethical approval

The study was conducted in accordance with the ethical standards of the institutional and/ or national research committee (Hacettepe University Ethics Board, date: 12 April 2007, reference number: HEK 07/16-21 and date: 5 June 2018, reference number: GO 18/473-31) and with the 1964 declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all patients or their parents/ legal guardians.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: ZRO, TŞE, ATA, TRG; data collection: EY, NK, NE, HSŞ, VŞ, GÜ, AİY, AAK, HÇ, AKB, HY, AÇ, SU, AŞŞ, DÖ, DUA, GKÖ, ED, AB, EB, ŞÇ, NS, İİ, ED, GDT, SEP, AÖ, KH, GK, MH, MK, ZT, HY, GÖ, ET, DC, PK, GC, MK, ŞÖ, EÇ, NÇ, SP, GC, UÖ, DD; analysis and interpretation of results: ZRO, TŞE, ATA, TRG; draft manuscript preparation: ZRO, TŞE, ATA, TRG, DD. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Assessment of the changing trends in maternal knowledge about management of fever and antibiotic use in the last decade in Türkiye

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ABSTRACT

Background. The wrong attitudes of parents on fever create a basis for unnecessary drug use and increased workload. The study was conducted to evaluate the knowledge and attitudes concerning fever and antibiotic use and demonstrate the changes in the last decade.

Methods. This cross-sectional study was composed of two parts, and a total of 500 participants were included. Group 1 (the new group, 50.0%) consisted of 250 participants who participated in the study between February 2020 and March 2020 and Group 2 (the old group, 50.0%) consisted of 250 participants who participated in the study between February 2010 and March 2010. All participants share the same ethnic properties and had been visiting the same center for similar reasons. A validated, structured questionnaire assessing the management of fever and antibiotic use was administered to all mothers.

Results. According to the fever assessment scoring, maternal knowledge of fever and its management in children significantly increased ($p < 0.001$). The antibiotic assessment score also increased in 2020 ($p = 0.002$).

Conclusions. The public spotlight on the erroneous use of antibiotics and the management of febrile illnesses seems to be promising. Improving maternal/parental educational status and informational advertisements can enhance parental knowledge concerning fever and antibiotic use.

Key words: fever, antibiotics, Mother's knowledge, the public spotlight.

Fever is a common reason for seeking medical attention, constituting up to 30% of visits to both primary care units and pediatric emergency departments.[1-3] Even though most febrile periods in children are benign, it remains a problem that most parents panic about. Inadequate provision of information to parents of children with febrile illnesses by healthcare providers may threaten trust in physicians, ultimately leading to treatment failures.[4,5] Wrong attitudes of parents on fever create a basis for unnecessary drug use and increased workload.[6] Wunderlich introduced the use of a mercurial axillary thermometer in 1851 and measured the axillary temperature in 25,000 patients and stated the average body temperature to be 37.0°C, ranging from 36.2°C to 37.5°C. Wunderlich defined temperatures above 37.5°C as "the territory of fever" and 38.0°C as fever. According to the World Health Organization (WHO), hyperpyrexia is defined as having a temperature above the normal range, and is accepted as 38°C and above for all age groups.[7]

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Antibiotic misuse is an ongoing problem in many countries. According to WHO, 80% of antibiotic consumption occurs in the community, with 20%–50% of such medications being improperly used.[8] This leads to antimicrobial resistance, defined as the ability of bacteria and other microorganisms to resist the effects of an antibiotic to which they were once sensitive.[9]

Unlike most physicians dealing with other specialties of medicine, pediatricians communicate not only with the patient but also with the parents. The insufficient knowledge of parents on the course of the disease may present as difficulty in history taking by the physicians. Several qualitative studies have shown evidence that on some occasions, parental anxiety in dealing with fever in a child increases by ineffective communication with healthcare workers.[10,11] Moreover, several medical reviews have indicated that parental knowledge of fever and antibiotics is insufficient in many countries.[12] To gain control, the Turkish Ministry of Health launched public service broadcasting to inform parents about fever and antibiotics in 2018. The study was conducted to evaluate the knowledge and attitudes concerning fever and antibiotic use and demonstrate the changes in the last decade.

Material and Methods

This cross-sectional study was composed of two parts, and 500 participants were included. The first part consisted of 250 mothers visiting outpatient pediatric clinics in Göztepe Training and Research Hospital, a large tertiary care clinic, between February 2010 and March 2010.[13] The second part consisted of 250 mothers sharing the same ethnic properties and visiting the same center between February 2020 and March 2020. The same validated questionnaire was employed among both populations. The questionnaire was adapted from several studies and consisted of six parts: (I) demographic characteristics of the parents, (II) parental attitude regarding antibiotic use, (III) parental knowledge about the definition of fever, (IV) parental knowledge on managing fever, (V) parental knowledge about complications of fever and fever phobia, and (VI) tools used by parents to measure body temperature.[14]

Three areas were assessed to determine the mothers' socio-educational level: the economic and occupational level of the mother, family income level, and the number of children in the family. The data obtained were classified as follows to determine the mothers' socio-educational level: low (0–2 points), moderate (3–4 points), and high (5–6 points).

Fever knowledge score (FKS)

The study questionnaire included five questions assessing the mothers' knowledge of fever, the existence of a temperature-measuring tool, body temperature regarded as fever, the management of high fever, and the drugs given to reduce fever. The answers obtained were classified as follows to determine the mothers' level of knowledge about fever (fever knowledge score): low (0–2 points) and high (3–5 points).

Antibiotic assessment score (AAS)

The study questionnaire included six questions assessing the mothers' knowledge of antibiotics. The answers obtained were classified as follows to determine the mothers' level of knowledge of antibiotic use: low (0–4 points) and high (5–7 points).

The participants were recruited using the convenience sampling method. The inclusion criteria of the study were as follows: (I) the mothers must understand Turkish, (II) the mothers should have at least one child older than 1 day of age, and (III) the mothers must not have attended any health-related education programs. The exclusion criteria were as follows: (I) mothers who are healthcare-related workers and (II) those who have a child with a chronic illness (e.g., spina bifida, chronic renal failure, and epilepsy).

The Turkish Republic of Health Ministry started public service broadcasting on television and prepared informative brochures in 2018. These advertisements inform the public about antibiotics and antibiotic misusage. The population in 2010 did not encounter the broadcasted spotlights. The population in 2020 declared that they encountered these public service broadcastings and understood their contents at least once in their life.

The questionnaire was applied by the physicians to the mothers in meeting rooms after a brief explanation. Each participant was given 15–20 min to complete the questionnaire.

The validity and reliability of the questionnaire were confirmed using the Kuder–Richardson Formula 21. Significance was evaluated at $p < 0.05$ level.

All data obtained from the questionnaires applied between February 2010 and March 2010 and between February 2020 and March 2020 were compared, and statistically analyzed.

This study was reviewed and approved by the Institutional Ethical Committee of İstanbul Medeniyet University Medical Faculty, (report number 2020/0159). Written consent was obtained from all participants before the study procedures were started.

Statistical analysis

The 2007 Number Cruncher Statistical System (Kaysville, Utah, USA) program was used for statistical analysis. The Shapiro–Wilk test was used to examine the suitability of quantitative data for the distribution of quantitative variables. The Mann–Whitney U-test was used to compare nonparametric variables. In the comparison of qualitative data, the Pearson chi-square test and Fisher–Freeman–Halton test were used. Significance was set at a level of $p < 0.05$.

Results

Demographic Characteristics of the Respondents:

Of the 550 questionnaires distributed, 500 were completed (90.9% response rate). Group 1 (new group, 50.0%) consisted of 250 participants who participated in the study between February 2020 and March 2020 and Group 2 (old group, 50.0%) consisted of 250 participants who participated in the study between February 2010 and March 2010. All respondents were mothers (100%) in the two groups. Moreover, 52.0% and 42.8% of the participants in groups 1 and 2, respectively, were more than 20 years of age. The mean ages of the mother–child pairs were similar between the groups ($p > 0.05$). A statistically significant difference in the degree of maternal education was observed between the groups ($p = 0.004$). The number of mothers with primary school educational level in Group 2 (68.4%) was higher than that in Group 1 (54.0%) ($p < 0.001$). No statistically significant difference in the number of children in families between the two groups ($p > 0.05$). The monthly income of the families in each group was also not statistically different ($p > 0.05$).

Socio-educational level scores were calculated. A statistically significant difference in the socio-educational level scores was observed between the two groups ($p = 0.005$): the scores in Group 1 were higher than those in Group 2.

Evaluation of maternal knowledge of fever and management

The device used to measure body temperature was significantly different between the two groups ($p < 0.01$). The proportion of mothers using a digital thermometer in Group 1 (74.4%) was higher than that in Group 2 (41.6%). In Group 2, the proportion of mothers who manually measure body temperature (36.6%) was higher than that in Group 1 (5.2%).

Statistically significant differences in the definition of fever and its management were observed between the two groups ($p < 0.01$). Salicylate usage as an antipyretic drug significantly decreased in 10 years. The proportions of mothers who use salicylate were 1.6% and 8.0% in groups 1 and 2, respectively (Table I). Fever knowledge scores were also calculated. (Table II). A statistically significant difference in the fever knowledge scores was observed between the two groups ($p < 0.01$); the scores in Group 1 were higher than those in Group 2.

Evaluation of knowledge and attitudes on antibiotic usage

The proportion of mothers who favored antibiotic use for viral infections was comparable between groups 1 and 2. No significant difference in the use of antibiotics for treating diarrhea or the common cold was observed between the two groups ($p > 0.05$). The duration of antibiotic use according to the prescription was statistically different between the two groups ($p < 0.01$). In Group 1 (88.4%), the number of mothers using antibiotics according to their prescription was higher than that in Group 2 (58.4%). Attitudes of mothers towards the expectancy of antibiotic prescription significantly changed in 10 years ($p < 0.01$). Furthermore, 94% of the participants in Group 1 use their prescriptions for other drugs even if they were not prescribed antibiotics. Proper usage of antibiotics significantly improved in Group 1 compared with that in Group 2 (Table III).

A statistically significant difference in AAS was observed between the two groups ($p < 0.01$). The scores in Group 1 were higher than those in Group 2 (Table IV).

Table I. Evaluation of fever knowledge, attitudes, and management.

		Total (n=500)	Group 1 (n=250)	Group 2 (n=250)	*p*
Device for measuring body temperature	Digital thermometer	290 (58.0)	186 (74.4)	104 (41.6)	[a]0.001*
	Mercury thermometer	75 (15.0)	22 (8.8)	53 (21.2)	
	Touching by hand (manual)	105 (21.0)	13 (5.2)	92 (36.8)	
	No fever measurement device	30 (6.0)	29 (11.6)	1 (0.4)	
Definition of fever	35°C	15 (3.0)	3 (1.2)	12 (4.8)	[a]0.001*
	36-36.9°C	44 (8.8)	20 (11.2)	24 (9.6)	
	37-37.9°C	157 (31.4)	70 (28.0)	87 (34.8)	
	38-39°C	259 (51.8)	148 (59.2)	111 (44.4)	
	≥39°C	25 (5.0)	9 (3.6)	16 (6.4)	
Causes of fever phobia	No complication	22 (4.4)	16 (6.4)	6 (2.4)	[a]0.001*
	Seizure	421 (84.2)	220 (88.0)	201 (80.4)	
	Stroke	13 (2.6)	1 (0.4)	12 (4.8)	
	Brain injury	34 (6.8)	12 (4.8)	22 (8.8)	
	I have no idea	10 (2.0)	1 (0.4)	9 (3.6)	
Managment of fever	Undressing	220 (44.0)	152 (60.8)	68 (27.2)	[a]0.001*
	Warm water bath	160 (32.0)	55 (22.0)	105 (42.0)	
	Giving antipyterics	86 (17.2)	34 (13.6)	52 (20.8)	
	Emergency room visit without intervention	30 (6.0)	9 (3.6)	21 (8.4)	
	Giving an antibiotic	4 (0.8)	0 (0)	4 (1.6)	
Use of anti-pyretic in management of fever	Ibuprofen	84 (16.8)	44 (17.6)	40 (16.0)	[a]0.001*
	Acetaminophen	328 (65.6)	183 (73.2)	145 (58.0)	
	Salicylate	24 (4.8)	4 (1.6)	20 (8.0)	
	No idea	64 (12.8)	19 (7.6)	45 (18.0)	

[a]Pearson Chi-Square Test, [c]Fisher Freeman Halton Test, *p<0.05

Table II. Fever knowledge scores.

	Total (n=500)	Group 1 (n=250)	Group 2 (n=250)	*p*
Min-Max (Median)	0-5 (3)	0-5 (4)	0-5 (3)	[b]*0.001***
Mean ± standard deviation	3.06±1.36	3.74±1.09	2.71±1.28	
Low score (0-2), n (%)	128 (25.6)	28 (11.2)	100 (40.0)	
High score (3-5), n (%)	409 (81.8)	222 (88.8)	150 (60.0)	

[b]Mann Whitney U Test, **p<0.01

Table III. Evaluation of knowledge and attitudes of antibiotic usage, n (%)

		Total (n=500)	Group 1 (n=250)	Group 2 (n=250)	*p*
Antibiotic indications	Diarrhea	48 (9.6)	25 (10.0)	23 (9.2)	[a]0.595
	Flu	121 (24.2)	65 (26.0)	56 (22.4)	
	All	56 (11.2)	24 (9.6)	32 (12.8)	
	None	275 (55.0)	136 (54.4)	139 (55.6)	
Antibiotics complications	No complications	12 (2.4)	4 (1.6)	8 (3.2)	[a]0.484
	Have complications	464 (92.8)	235 (94.0)	229 (91.6)	
	Should not be used	24 (4.8)	11 (4.4)	13 (5.2)	
Antibiotics usage attitudes	Use it as prescribed	367 (73.4)	221 (88.4)	146 (58.4)	[a]0.001**
	Use until the bottle runs out	72 (14.4)	16 (6.4)	56 (22.4)	
	Use until the fever subsides back to normal	61 (12.2)	13 (5.2)	48 (19.2)	
Antibiotics can treat all types of infections	Yes	34 (6.8)	15 (6.0)	19 (7.6)	[a]0.477
	No	466 (93.2)	235 (94.0)	231 (92.4)	
Attitudes when antibiotics were not prescribed	Change the doctor	71 (14.2)	14 (5.6)	57 (22.8)	[a]0.001**
	Use an antibiotic recommended.	10 (2.0)	1 (0.4)	9 (3.6)	
	Use the other drugs prescribed	419 (83.8)	235 (94.0)	184 (73.6)	
Antibiotic can prevent febrile seizure	Yes	141 (28.2)	79 (31.6)	62 (24.8)	[a]0.091
	No	359 (71.8)	171 (68.4)	188 (75.2)	

[a]Pearson Chi-Square Test, **p<0.05

Table IV. Antibiotic assessment scores.

	Total (n=500)	Group 1 (n=250)	Group 2 (n=250)	*p*
Min-Max (Median)	1-7 (5)	2-7 (6)	1-7 (5)	[a]*0.002***
Mean ± standard deviation	5.25±1.54	5.48±1.41	5.02±1.64	
Low score (0-4), n (%)	153 (30.6)	59 (23.6)	94 (37.6)	
High score (5-7), n (%)	347 (69.4)	191 (76.4)	156 (62.4)	

[b]Mann Whitney U Test, **p<0.01

Discussion

To the best of our knowledge, this is the first study that has compared data on maternal perspectives on fever, antibiotic knowledge, and attitudes in Türkiye between 2010 and 2020. Moreover, it is the first study that reveals a chance to see the effectiveness of public spotlights on antibiotic use since 2018 in Türkiye. Therefore, these findings can be useful for healthcare professionals and healthcare-related policymakers to better understand the level of knowledge on fever and antibiotic use in the local community, which may later help develop strategies to address related issues.

When we analyzed the data obtained between 2010 and 2020, monthly household income was comparable between the two groups. However, in group 1, a significant increase in maternal educational status was observed. As can be appreciated, mothers should have a sound understanding of what fever is so that they can act accordingly in managing their febrile children. The ratio of those who correctly determined fever in this study was 40% in 2010; this rate increased to 65% after 10 years. In 2010, the mothers' educational level and socio-educational level scores were risk factors for low fever knowledge scores. The increase in the socio-educational level scores over the past decade explains the significant increase in fever definition and fever knowledge score. Kelly et al.[15] in 2019 and AlAteeq et al.[16] in 2015 found this ratio to be 64% and 76% in English and Saudi populations, respectively. Although this improvement is promising, it remains insufficient compared with those observed in other countries. To prevent the wrong definition of fever, parents should avoid determining fever by touching. In 2010, 36% of the participants measured the fever of their children by touching, and this practice was employed by 5.1% of the participants in 2020. So, this study demonstrated that the determination of fever by touching significantly decreased after 10 years. Digital thermometers were the most preferred fever-measurement device in 2020 (74.4%). Taştan et al.[17] in 1998 have found that 28% of mothers used a thermometer compared with 72% in the study by Baysoy et al.[18] 2005. , 73% in the study by Kürügöl et al.[19] 1995, 15% in the study by Parmar et al.[20] 2001, 50% in the study by Arica et al.[21] 2011, and 45.8% in the study by Yavuz et al. 2017.[22] Fever phobia is the most important factor for parents to consult emergency rooms.[11] The prevention of fever phobia can decrease redundant emergency room applications In a seminal 1980 study by Schmitt, who originated the phrase "fever phobia," it was discovered that parents generally had a negative perspective of fever, with 94% of them feeling it could cause injury, 63% believing it could cause major harm, and 18% believing it may cause brain damage. A follow-up study by Crocetti et al. demonstrated that 91% of parents were "worried" and 56% were "anxious" about the potential harm of fever, with seizures (32%), brain damage (21%), and death (14%) frequently mentioned.[23-25] In this study, febrile seizures remain the most important cause of fever phobia (88.8%). Nevertheless, maternal perception of fever as a cause of death or brain damage significantly decreased in 2020 (4.8%) compared with that in 2010 (8.8%). Salicylate use as an antipyretic drug dramatically decreased from 8% to 1.6%. This finding is important since the avoidance of salicylate is vital in preventing Reye syndrome, an important cause of hepatic coma, hypoglycemia, and death during viral infections.[26,27] The increase in the education level of the mothers without an increase in the socioeconomic level made us think that there was an improvement in the quality of education in the population independent of the economy. This statistical increase in education level may have contributed to the increase in health literacy. This may have a positive effect on the AAS and FKS.

In the past decade, most respondents did not clearly understand the purpose of taking antibiotics. Moreover, most mothers also believed that antibiotics could be used to treat all types of infections, including viral infections, such as flu and diarrhea.[28] This study indicated that this misconception has not changed over

the last decade. Antibiotic prescription for viral infections remains expected from parents in 2020. In contrast, this study demonstrated that maternal pressure on physicians to prescribe antibiotics decreased. However, antibiotic misusage significantly decreased compared with data obtained in 2010; it remains an ongoing problem in 2020. This is a good but not enough improvement for preventing antimicrobial resistance. How to raise awareness among the public regarding antibiotic knowledge remains an important research topic. Wilson et al. 2019 have demonstrated that education given by healthcare professionals was inadequate to improve the status of parents about this issue.[29] The Turkish Republic of Health Ministry started broadcasting public spotlights on the television nearly every week since 2018. Moreover, informative brochures were prepared to encompass the entire country. All these seem promising and significantly increase the AAS ($p < 0.001$). In France, the same has been practiced since 2005. Warembourg et al. 2020 have demonstrated that the adherence rate of the pediatric population to anti-infective drugs prescribed was 89% in France.[30] In this study, the rate of adherence to prescription was 88.4% in 2020 and 58.4% in 2010 ($p < 0.001$). The increased degree of maternal education in the last decade may also have contributed to the positive outcomes assessed in this study. Additionally, improvement in the AAS and FKS are multifactorial, such as the increase in the level of education in the society, the ease of access to information resources over the years, and the effect of social media, together with the public service announcements. Because of this, further studies are needed to reach hard endpoint conclusions on the efficacy of the spotlights on fever and antibiotic use, which are actively broadcasted in the media.

The responses of the participants may not be totally unbiased owing to the closed questionnaire design. The possibility that the development of technological facilities over time and the existence of many environmental factors that we cannot control have affected our results should also be considered. This study demonstrated that fever knowledge and AAS increased in the last decade. Antibiotic misusage remains an ongoing problem in 2020. Spotlights broadcast on television about these issues may have a positive influence on the public. Mothers' fever and antibiotic use knowledge and attitudes are important for countries to refer the right treatment and prevent inadvertent use of medications. Improvement of maternal/parental educational status and informational advertisements can improve fever and antibiotic knowledge scores.

Ethical approval

This study was reviewed and approved by the Institutional Ethical Committee, Medical Faculty, Istanbul Medeniyet University (report number 2020/0159). Written consent was obtained from all participants.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: SGS, ME; data collection: SGS, ME, EYK, UB,YÇ. Analysis and interpretation of results: SGS, UB, Draft manuscript preparation: SGS, ME, EYK, YÇ. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Pediatricians' attitudes, practices, and perceived barriers to school readiness

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ABSTRACT

Background. School readiness (SR) has been adopted by the American Academy of Pediatrics (AAP) as a component of health supervision, but the medical community's role is unknown. We evaluated the pediatricians' attitudes, practices, and perceived barriers to SR.

Methods. This multicenter, cross-sectional descriptive study was performed among 787 general pediatricians, pediatric residents, subspecialists, and subspecialty fellows. A 41-item survey was administered.

Results. Forty-nine point two percent of the pediatricians defined SR as a multidimensional issue, as outlined by the AAP, whereas 50.8% defined it as the child's set of skills or passing the SR tests. Three-quarters of pediatricians believed that SR assessment tests are necessary before starting school, and children who do not appear ready should wait a year. To promote SR, the rates of usually fostering at least four of the five "Rs" (reading, rhyming, routines, rewarding, relationships) and integrating developmental surveillance into daily practice were 37.8% and 23.8%, respectively. Only 2.2% of pediatricians usually inquired about eight adverse childhood experiences (ACEs), and 68.9% did not usually ask about any. Usually fostering at least four of the five "Rs" was associated with usually integrating developmental surveillance ($p<0.001$), usually inquiring about each ACE ($p<0.001$), and being perceived as responsible for promoting SR ($p<0.01$). Training on SR during pediatric residency was 2.7%. Time constraints and insufficient knowledge were the most common barriers.

Conclusions. Pediatricians were not familiar with the concept of SR and had some misconceptions. There is a need for additional training regarding pediatricians' roles in promoting SR along with addressing multiple, modifiable barriers within the health system.

Key words: School readiness, pediatrician, adverse childhood experiences, developmental surveillance, barriers.

The common goal of the Pediatric and Early Childhood Education (ECE) fields is to support optimal child development during the first years of life.[1] One of the measures for maximizing developmental potential is school readiness (SR). SR is a multidimensional issue that includes not only children's readiness for school but also schools' readiness for children as well as the family and community supports and services that contribute to school success.[2,3] Being ready for school is strongly associated with higher academic achievement, lower dropout rates, lower teen pregnancy and

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juvenile arrest rates, and better health, social, and economic outcomes in adulthood.[4-7]

Among the 17 Sustainable Development Goals published by the United Nations, the fourth goal is "By 2030, ensure access to quality early childhood development, care, and preschool education so that all girls and boys are ready for school".[8] Despite a significant increase in preschool enrollment in Türkiye over the past ten years, school enrollment rates for children between the ages of three and five have fallen of both the OECD (the Organisation for Economic Co-operation and Development) average and the goals set by the Ministry of National Education.[9,10] Children from low-income families and those born to less-educated mothers are less likely to access preschool education.[11] Türkiye has a limited publicly funded, consistent, and comprehensive ECE system to support the SR of these disadvantaged children. General pediatricians, pediatric residents, pediatric subspecialists, and subspecialty fellows have many opportunities to reach almost all preschool-aged children, especially those affected by poverty and inadequate ECE, within the healthcare system in Türkiye, as in other countries. During the preschool years, children visit general pediatricians an estimated minimum of ten times for a variety of healthcare needs, including vaccination, nutrition, and physical-growth monitoring, as well as management of acute or chronic diseases.[12] Pediatric subspecialists and subspecialty fellows are also well-positioned to reach children with chronic health conditions who are at higher risk of experiencing social-emotional, cognitive, and language difficulties, as well as not being ready for school.

The American Academy of Pediatrics (AAP) has adopted SR as a component of health supervision and developed a policy statement regarding the roles and responsibilities of pediatricians in promoting SR.[2,3] The AAP recommends pediatricians promote healthy parent-child relationships and early learning environments by fostering the 5 "Rs" of early education ("reading" aloud together daily; supporting reciprocal and nurturing "relationships"; "rhyming", talking, playing together; establishing "routines"; "rewarding" everyday success), informing families about safe and supportive preschool education, limiting screen exposure, as well as providing optimal physical well-being.[3] According to the policy statement, to promote SR, pediatricians should also focus on the developmental and behavioral issues during pediatric visits and refer children at risk to community services and evidence-based family support programs.[3] Without early detection and appropriate intervention for children with developmental difficulties in their first years of life, these children are unlikely to be ready for school.[13] The AAP statement also explicitly states that in order to enter school ready to learn, children need protection from injury, abuse, and neglect as well as from exposure to violence and discrimination.[14] So, the AAP recommends pediatricians screen for adverse childhood experiences (ACEs) in order to address inadequacies in SR that may emanate from a toxic home environment.[14]

SR refers to readiness for the first year of formal primary education. Since formal primary education in the United States of America (USA) begins with kindergarten at around age 5, the term "school readiness" has been used for kindergarten by the AAP, which predicts subsequent primary SR.[3,14] However, in Türkiye, as in Europe, China, and Canada, children start their formal education at six years of age in primary education schools, and kindergarten education is facultative.[15,16] Therefore, SR refers to readiness for primary school in our study.

Despite the AAP's recommendations, pediatricians' current attitudes, practices, and perceived barriers to SR are unknown. Therefore, this study aimed to evaluate pediatricians' familiarity with the concept of SR, reveal their attitudes and clinical practices on this issue, investigate the variables that are effective in their clinical practices supporting SR, and identify the barriers they perceive when promoting SR.

Material and Methods

Survey administration

This multicenter, cross-sectional descriptive study was conducted at seven training and research hospitals in Türkiye, specifically in the provinces of Ankara, Izmir, Istanbul, and Adana. After approval by the Ankara Bilkent City Hospital Ethics Committee (01.09.2021; E2-21-758), the survey was distributed online using "Google Docs" or handed out from September 10, 2021, to October 10, 2021. The research was conducted on volunteer pediatricians, pediatric residents, pediatric subspecialists, and subspecialty fellows. Although this study was carried out primarily in these seven hospitals, an announcement with a direct link to "Google Docs" was also made through the WhatsApp groups of pediatricians. So, pediatricians who wanted to participate in the study individually from other hospitals and private practices were also included. As well as well-child care, chronic healthcare visits are crucial opportunities to address ECE inequities and support SR, so we included general pediatricians, pediatric residents, pediatric subspecialists and subspecialty fellows in the "pediatrician" group. The exclusion criterion was the failure to complete the survey. Informed consent was taken from pediatricians as seen in supplementary appendix.

Survey questions

After an extensive literature review, the study team developed a 41-item survey. A preliminary study was conducted on a sample of 20 pediatric residents to evaluate the comprehension of questions. Survey revisions (e.g., format modification, item expression, response options) were made with the feedback to ensure ease of understanding and implementation.

The survey was grouped into five sections: (1) Demographic information and practice characteristics; (2) Beliefs and attitudes about SR; (3) Clinical practices to promote SR; (4) Training and competence for SR; and (5) Perceived barriers to supporting SR (Supplementary Appendix). It consisted of five open-ended, one yes-no, four multiple choice, eleven 5-point Likert scale, seventeen 4-point Likert scale, and three 3-point scale questions. It took approximately seven minutes to fill out.

Demographic information and general practices such as age, gender, title, having the experience of starting school as a parent, years in practice, the average number of children examined in the 0-5 age group per day, and the average time of service provided for each child were elicited with one yes-no and five open-ended questions.

To evaluate how pediatricians perceive the components of SR, they were asked to choose the best definition of SR from a multiple-choice question, adapted from the study of Perrin et al.[17] A series of eleven positively worded statements with responses on a 5-point Likert scale ranging from "strongly agree" to "strongly disagree" was used to assess beliefs and attitudes about SR. "Strongly agree/agree" responses were compared to "not sure/disagree/strongly disagree".

The clinical practices to promote SR were evaluated with the following: fostering the 5 "Rs", limiting screen time, advising preschool education, identifying developmental-behavioral issues, and inquiring about ACEs. Questions, including clinical practices relating to fostering the 5 "Rs", limiting screen time, and advising preschool education were formed from a 4-point Likert scale (1: Never, 2: Rarely, 3: Sometimes, 4: Usually). Pediatricians questioned their clinical practices regarding developmental-behavioral issues with two multiple-choice and two 4-point Likert scale (1: Never, 2: Rarely, 3: Sometimes, 4: Usually) questions. Inquiring about ACEs (parental mental illness, parental separation or divorce, physical or sexual abuse, physical or emotional neglect, hostile/rejecting parenting, domestic violence experience, parental alcohol or drug use, incarcerated caregiver) elicited with eight 4-point Likert scale (1: Never, 2: Rarely, 3: Sometimes, 4: Usually) questions.[18,19] Responses

were dichotomized to compare "usually" with "sometimes/rarely/never". Whether pediatricians' had received training during residency and their perceived competency on SR were evaluated with 3-point scale (a: Yes, b: No, c: Not sure) questions and responses were dichotomized such as "yes" to compare to "no/not sure". A multiple-choice question was used to obtain information on the barriers perceived by pediatricians in supporting SR.

Sample size

The sample size with a 5% margin of error and a 95% confidence level was 370 and 377 for a population of 10000 and 20000, respectively. When the number of active pediatricians (general pediatricians, pediatric residents, pediatric subspecialists, and subspecialty fellows) is estimated to be between 15000 and 20000 in our country, it is aimed to reach at least 377 pediatricians.[20]

Statistical analyses

Statistical analysis was performed with the SPSS statistical package (v. 20.0 for MAC). The chi-square test was used to compare categorical variables. A t-test and Mann-Whitney U test were used to compare two groups with a normal and non-normal distribution of data, respectively. Kruskal-Wallis test was used to compare more than two groups with non-normal distributions. A p-value <0.05 was accepted as statistical significance. A chi-square test was used to compare general pediatricians/residents and subspecialists/fellows in terms of their beliefs and attitudes, clinical practices, previous training related SR, perceived competence, and responsibility.

Results

Demographic characteristics of pediatricians

A total of 787 pediatricians responded to the survey. Overall, the proportion of general pediatricians, pediatric residents, pediatric subspecialists, subspecialty fellows was 37.4% (n=294), 27.2% (n=214), 20.8% (n=164) and 14.6% (n=115), respectively. The median age of the pediatricians was 35.5 (24-65), and 74.7% were female. Among the pediatricians, 46.7% (n=367) had previously experienced starting their child at school. The median practice year in the pediatrics field was 7 (1-45) years. Three-hundred-eleven (39.5%) pediatricians had more than ten years of experience. The pediatric residents were in the median 3rd (1-4) year of training. Pediatricians reported that they served a median of 25 (2-200) children aged 0-5 years and their families per day, with a median of 10 (2-60) minutes for each child.

The familiarity with the concept of SR

Three hundred ninety-one (49.7%) pediatricians identified the definition of SR as a child's skill set for school success, 1.1% (n=9) identified as having a score on SR tests ≥ 70; the remaining 49.2% (n=387) identified as outlined by AAP (a multidimensional characteristic that includes the child's skills, the school's adaptability, and family/community support).

The beliefs and attitudes about SR

Almost all (96.4%) pediatricians agreed that SR is significant for long-term academic success. Less than half (45.5%) believed that readiness could be measured easily. Approximately three-quarters of the pediatricians believed that a SR assessment test should be conducted for each child before starting school, and children who do not appear ready for school should wait a year. While 40.8% of pediatricians agreed that they are responsible for promoting SR, 61.1% agreed that they have a responsibility to advocate for access to services (Table I).

The median year of experience in the pediatrics field was higher in pediatricians who believed that SR could be measured easily (median year of experience 9 (1-45) vs. 7 (1-45), p=0.000) and children who were not ready for school should wait a year (median year of experience 8 (1-45) vs. 7 (1-40), p=0.016). Pediatricians with higher practice years were also more likely to agree

Table I. Pediatricians' beliefs and attitudes about school readiness

	Strongly Agree n (%)	Agree n (%)	Not sure n (%)	Disagree n (%)	Strongly Disagree n (%)
School readiness is significant for long-term academic success.	665 (84.5)	94 (11.9)	12 (1.5)	11 (1.4)	5 (0.6)
School readiness can be measured easily.	68 (8.6)	290 (36.8)	170 (21.6)	223 (28.3)	36 (4.6)
Before starting school, a school readiness assessment test should be conducted for each child.	369 (46.9)	251 (31.9)	95 (12.1)	63 (8.0)	9 (1.1)
Children who do not appear ready for school should wait a year.	293 (37.2)	276 (35.1)	140 (17.8)	62 (7.9)	16 (2.0)
The achievement gap between children with and without school readiness closes over time.	57 (7.2)	267 (33.9)	203 (25.8)	193 (24.5)	67 (8.5)
It is the school's responsibility to ensure all children's educational needs who are old enough to attend school legally, regardless of their readiness status.	157 (19.9)	220 (28.0)	153 (19.4)	164 (20.8)	93 (11.8)
Children who attend preschool are more successful in school than those who do not.	375 (47.6)	235 (29.9)	110 (14.0)	44 (5.6)	23 (2.9)
Pediatricians are responsible for promoting school readiness.	99 (12.6)	222 (28.2)	192 (24.4)	184 (23.4)	90 (11.4)
Pediatricians are responsible for advocating access to services to support school readiness.	218 (27.7)	263 (33.4)	146 (18.6)	109 (13.9)	51 (6.5)
Early identification and intervention of developmental difficulties promote school readiness, success, and learning outcomes.	598 (76.0)	180 (22.9)	8 (1.0)	1 (0.1)	0
Adverse childhood experiences cause toxic stress and negatively affect brain development, learning, and school readiness in preschool years.	378 (48.0)	346 (44.0)	55 (7.0)	6 (0.8)	2 (0.3)

with their responsibility for promoting (median year of experience 8 (1-45) vs. 7 (1-45), p=0.014) and advocating SR (median year of experience 8 (1-45) vs. 7 (1-45), p=0.024). Pediatricians who had previously experienced starting their child at school and male pediatricians were more likely to agree that readiness for school can be measured easily (p=0.000 and p=0.006, respectively).

Clinical practices to promote SR

The frequencies of fostering the 5 "Rs" suggestions, advising to limit screen time, and advising to attend preschool education are shown in Table II. Approximately one-fourth (24.8%) of pediatricians reported that they did not usually foster any of the 5 "Rs" as a part of daily practice, while 37.8% (n=298) usually fostered at least four of the 5 "Rs". Pediatricians who usually fostered at least four of the 5 "Rs" were older (median age 37 (25-68) vs. 34 (25-64), p=0.001), had longer duration of health visit for each child (median service duration 10 (2-60) vs. 10 (2-50) minutes, p=0.001), had more frequently experienced their children's beginning to school (55.2% vs. 40.9%, p=0.002), and had more experience in the pediatrics field (median year of experience 9 (1-42) vs. 6 (1-40), p=0.000) compared to those who did not usually foster any of the 5 "Rs". There was no gender difference between these two groups (female sex ratio 75.1% vs. 73.3%, p=0.663). Of the pediatricians, 81.4% usually recommend limiting screen time. Half of the pediatricians (52.3%) stated that they usually advise attending

Table II. The frequencies of the pediatricians giving 5 "Rs" suggestions, advising to limit screen time and to attend preschool education.

	Usually n (%)	Sometimes n (%)	Rarely n (%)	Never n (%)
Read aloud to your child daily.	354 (45.0)	255 (32.4)	127 (16.1)	51(6.5)
Provide sensitive, tolerant, reciprocal, and nurturing relationships with your child.	416 (52.9)	219 (27.8)	118 (15)	34 (4.3)
Sing to your child, tell stories, talk, play, and rhyme.	406 (51.6)	222 (28.2)	119 (15.1)	40 (5.1)
Establish routines around meals, sleep, and playtimes.	401 (50.9)	237 (30.1)	118 (15.0)	31 (3.9)
Praise your child as a reward for everyday successes.	377 (47.9)	242 (30.7)	134 (17.0)	34 (4.3)
Limit screen time.	641 (81.4)	112 (14.2)	28 (3.6)	6 (0.8)
Provide your child to attend preschool education.	412 (52.3)	244 (31.0)	84 (10.7)	47 (6.0)

preschool education before primary school, while 31.0% sometimes advise.

Almost all (98.9%) pediatricians agreed that timely identification of developmental difficulties and appropriate referrals for early intervention programs positively affect SR, success, and learning outcomes, and only 23.8% (n=187) reported that they integrate developmental surveillance into their practices. The frequency of using a validated tool for developmental assessment was reported as usually, sometimes, rarely, and none by 10.8%, 17.4%, 25.4%, and 46.4% of pediatricians, respectively. Speech and language delay, global developmental delay, behavioral problems, and attention-deficit/hyperactivity disorder were reported as the most common developmental-behavioral difficulties limiting SR by 24.9%, 24.4%, 22.5%, and 17.9% of pediatricians, respectively. Pediatricians reported that they referred the child who does not appear ready for school to a developmental and behavioral pediatrician (40.4%), child development specialist (34.6%), child psychiatrist (19.6%), preschool or kindergarten services (2.0%), child neurologist (1.0%) and others (2.4%).

Most pediatricians (92.0%) agreed that ACEs cause toxic stress and disturb brain development, learning, and SR in the preschool years. However, only 2.2% of pediatricians usually inquired about 8 ACEs, 28.9% usually asked for some, and 68.9% did not usually ask about any. Pediatricians who usually asked for some of the ACEs had a longer duration of health visit for each child (median service duration 10 (3-60) vs. 10 (2-50) minutes, p=0.000) compared to pediatricians who did not usually ask about any. There was no difference between these two groups in terms of age (median age 36 (24-70) vs. 35 (25-64), p=0.126), gender (female sex ratio 79.0% vs. 72.9%, p=0.067), years of experience in the pediatrics field (median year of experience 8 (1-45) vs. 7 (1-40), p=0.055), and prior experience of starting their children at school (47.5% vs. 46.7%, p=0.825). The ACEs that pediatricians asked for most usually were parental separation or divorce (17.4%) and physical or emotional neglect (17.3%).

Training, perceived competency, and responsibility for SR

Very few pediatricians (2.7%) reported that they received training on SR in their pediatric residency. Only 11.7% of the pediatricians considered that they had sufficient knowledge about SR, and 10.8% perceived themselves as competent in assessing a child's readiness for school. The rates of usually fostering at least four of the 5 "Rs" in routine practice (61.9% vs. 34.7%, p=0.001), usually performing developmental surveillance (38.0% vs. 21.9%, p=0.001), and usually using a validated tool for developmental assessment (18.5% vs. 9.8%, p=0.012) were significantly higher in pediatricians who considered themselves to have sufficient knowledge about SR than those who did not. Although the rate of

usually asking some of the ACEs was higher in pediatricians who considered themselves to have sufficient knowledge, the difference was not statistically significant (38.0% vs. 30.0%, p=0.118). Pediatricians who considered themselves to have sufficient knowledge more frequently agree that SR could be measured easily (59.8% vs. 43.5%, p=0.003), children who attended preschool education are more successful in school (85.9% vs. 76.4%, p=0.041), and pediatricians are responsible for promoting SR (51.1% vs 39.5%, p=0.033), compared to those who did not. The rate of agreement with the necessity of a SR assessment test for each child before school (79.3% vs. 78.7%, p=0.887) and the requirement of postponing the start of school for children who are not ready for school (80.4% vs 71.2%, p=0.062) were similar between groups. Other beliefs and attitudes were similar.

Usually fostering at least four of the 5 "Rs" in routine practice was significantly associated with usually integrating developmental surveillance (p<0.001), usually using a validated tool (p<0.001), and usually inquiring about each ACE (p<0.001). Also, pediatricians who usually foster at least four of the 5 "Rs" were more likely to have training on SR (p=0.006), perceive themselves as competent to assess SR (p<0.001) and be responsible for supporting (p<0.001) and advocating SR (p=0.002) (Table III).

The beliefs and attitudes, clinical practices, training, perceived competence, and responsibility about SR were similar between general pediatricians/pediatric residents and subspecialists/subspecialty fellows (p>0.05).

Perceived barriers to promoting SR

Pediatricians' perceived barriers to support SR were time constraints (72.3%), lack of knowledge about SR (56.7%), not bringing up this issue during health care visits by families (47.8%), families' not following the suggestions given (31.5%), confusion about which specialty or community resources to refer the child who is not ready for school (21.3%), not perceiving themselves as responsible for promoting SR (9.8%), and considering that this issue is mostly the responsibility of educators (0.5%).

Discussion

To the best of our knowledge, this is the first study that provides preliminary data regarding the implementation of the AAP's SR technical report recommendations by the medical community and reveals their role in promoting SR. The present study showed that AAP recommendations had not been well adopted in pediatric practices in Türkiye and significant barriers must be addressed.

Approximately 50% of the pediatricians defined SR as the child's set of skills rather than a multidimensional issue; only 49% described it as not only with the child but also with the family/community support and services, and schools' readiness for the child's individual needs and abilities. Pediatricians' knowledge of the roles of families, communities, and schools in SR is significant for anticipatory guidance, identifying high-risk children, referring to community resources, and providing effective advocacy. In our study, the pediatricians' perceptions relating to SR are grounded in the child's maturational process.

All children who are old enough to attend school legally are entitled to an appropriate education in the least restrictive environment. Most communities implement some form of "school readiness tests" to assess whether the child is ready for school or not. However, SR tests can easily be incorrectly applied and interpreted. When SR tests are administered by individuals who have a limited perspective on the variations of normal development or who have inadequate formal training in test administration, children can be wrongly identified as not ready for school.[3,21] Approximately two-thirds of the pediatricians in our study stated that a SR assessment test should be conducted for each child before starting school, and children who are not ready for school should wait a year to mature.

Table III. Clinical practices relating developmental problems and adverse childhood experiences, training competence, and perceived responsibility about school readiness, and their association with fostering the 5 "Rs".

	Fostering at least four of the 5 "Rs" in daily practice			
	Usually n=298 n (%)	Sometimes/ Rarely/Never n=489 n (%)	Total n=787 n (%)	p-value
Frequency of integrating developmental surveillance into clinical practice for early identification of developmental problems				
Usually	105 (35.2)	82 (16.8)	187 (23.8)	<0.001
Sometimes / Rarely/ Never	193 (64.8)	407 (83.2)	600 (76.2)	
Frequency of using a validated tool for developmental assessment				
Usually	54 (18.1)	31(6.3)	85 (10.8)	<0.001
Sometimes / Rarely/ Never	244 (81.9)	458 (93.7)	702 (89.2)	
Frequency of inquiring about adverse childhood experiences				
Parental mental illness				
Usually	64 (21.5)	31(6.3)	95 (12.1)	<0.001
Sometimes / Rarely/ Never	234 (78.5)	458 (93.7)	692 (87.9)	
Parental separation or divorce				
Usually	86 (28.9)	51 (10.4)	137 (17.4)	<0.001
Sometimes / Rarely/ Never	212 (71.1)	438 (89.6)	650 (82.6)	
Physical or sexual abuse				
Usually	66 (22.1)	42 (8.6)	108 (13.7)	<0.001
Sometimes / Rarely/ Never	232 (77.9)	447 (91.4)	679 (86.3)	
Physical or emotional neglect				
Usually	83 (27.9)	53 (10.8)	136 (17.3)	<0.001
Sometimes / Rarely/ Never	215 (72.1)	436 (89.2)	651 (82.7)	
Hostile/rejecting parenting				
Usually	45 (15.1)	19 (3.9)	64 (8.1)	<0.001
Sometimes / Rarely/ Never	253 (84.9)	470 (96.1)	723 (91.9)	
Domestic violence experience				
Usually	60 (20.1)	31 (6.3)	91 (11.6)	<0.001
Sometimes / Rarely/ Never	238 (79.9)	458 (93.7)	696 (88.4)	
Parental alcohol/drug use				
Usually	43 (14.4)	28 (5.7)	71 (9.0)	<0.001
Sometimes / Rarely/ Never	255 (85.6)	461 (94.3)	716 (91.0)	
Incarcerated caregiver				
Usually	32 (10.7)	12 (2.5)	44 (5.6)	<0.001
Sometimes / Rarely/ Never	266 (89.3)	477 (97.5)	743 (94.4)	
Received training on school readiness				
Yes	14 (4.7)	7 (1.4)	21 (2.7)	0.006
No/ Not sure	284 (95.3)	482 (98.6)	766 (97.3)	
Have enough information about school readiness				
Yes	57 (19.1)	35 (7.2)	92 (11.7)	<0.001
No/ Not sure	241 (80.9)	454 (92.8)	695 (88.3)	
Competent to assess a child's school readiness				
Yes	56 (18.8)	29 (5.9)	85 (10.8)	<0.001
No/ Not sure	242 (81.2)	460 (94.1)	702 (89.2)	
Pediatricians are responsible for promoting school readiness				
Agree/ Strongly Agree	142 (47.7)	178 (36.4)	320 (40.7)	<0.001
Not sure/ Disagree/ Strongly Disagree	156 (52.3)	311 (63.6)	467 (59.3)	
Pediatricians are responsible for advocating access to services to support school readiness				
Agree/ Strongly Agree	203 (68.1)	279 (57.1)	482 (61.2)	0.002
Not sure/ Disagree/ Strongly Disagree	95 (31.9)	210 (42.9)	305 (38.8)	

This remarkable result is worrisome when considering the inappropriate use of readiness tests, which may label children as "not ready" for school and keep them out of the benefits of the classroom environment, which is crucial for learning and peer interactions.[14]

Supportive parenting and learning home environments are considered to be the characteristics of ready families. A study conducted in a low-income population showed that parents find SR important and feel responsible for preparing their child for school.[22] However, the lack of knowledge of how to prepare their children for school was the most reported barrier to SR.[22] Research emphasized that parents identify pediatricians as the most trusted and helpful professionals and accept their advice about parenting and managing developmental and behavioral issues and want more guidance about learning, behavior, and development.[23-26] However, in our study, pediatricians agreed that it was their responsibility to advocate for children's access to services rather than to promote SR. Only 37.8% of pediatricians reported that they usually recommended at least four of the 5 "Rs". It was observed that the most common recommendation given to support SR was to limit screen time. This finding shows that pediatricians have a high level of awareness regarding screen time's detrimental effects on development but limited awareness regarding the 5 "Rs".

Although 98.9% of pediatricians agreed that early identification and intervention of developmental difficulties promotes SR, only one-fourth usually integrate developmental surveillance into their clinical practices. Approximately 90% of pediatricians usually rely heavily on their intuition and clinical judgment on developmental issues rather than using a validated tool. The rate of using a validated tool is far behind that of developed countries.[27,28]

Despite the fact that most pediatricians endorsed the fact that ACEs impair learning and SR, only 2.2% of them usually inquired about all 8 ACEs, and 68.9% did not usually ask about any. Our findings are compatible with a previous study from the USA, which reported that 32% of the pediatricians did not inquire about any ACEs; only 4% usually asked about all 7 ACEs (physical or emotional neglect was not included in their study questionnaire).[29]

The statistically significant findings showed that the pediatricians who gave more suggestions for the 5 "Rs" were more likely to identify developmental problems and ACEs in the present study. On the other hand, the previously received training on SR seems to be associated with giving more 5 "Rs" related suggestions in our study. However, since only a small number of pediatricians (n=14) within this group had training, this result can not be generalized. Consistently, the pediatricians who considered themselves to have sufficient knowledge about SR were more likely to foster the 5 "Rs", perform developmental surveillance, and use a validated tool for developmental assessment. But surprisingly, pediatricians who consider themselves to have sufficient knowledge about SR has also some misconceptions, especially about the application of SR tests for each child before school and the postponement of starting school for those who are not ready. These findings suggest that additional training on SR may foster pediatricians' knowledge, competence, and confidence and also lead to greater interest and involvement in clinical practice.

There are some barriers that pediatricians perceive when promoting SR. Similar to the previous studies on the identification and management of developmental and mental health issues from the USA, Israel, and Türkiye, our study also showed that lack of time during appointments and insufficient clinical knowledge were the most frequently cited barriers.[28,30-35] Because of the high patient load and busy schedules, many of the pediatricians reported not being able to provide detailed evaluations regarding developmental issues and SR. The median visit duration was 10 minutes and 72.3% of the pediatricians

reported not having enough time to promote SR. Moreover, our results showed that longer duration of health care visits for each child was associated with fostering at least four of the 5 "Rs" as usually and asking about some ACEs during the clinical practices. These results reflect that pediatricians may usually focus more on medical problems and have limited time to approach developmental issues and SR due to time constraints. Most pediatricians (97.3%) reported that they did not receive any formal education on SR during pediatric residency training. Moreover, most pediatricians did not perceive themselves as responsible for promoting SR. Perrin et al.[17] showed that a resident-focused SR curriculum increases pediatric residents' knowledge, confidence, and ability to manage concerns in clinical encounters. Topics relating to SR and pediatricians' role in promoting SR should be introduced into medical school and pediatric residency curricula. There is also a need for in-service training on SR for clinicians. Previous studies have shown that training programs for clinicians to enhance child development improve their practices.[36,37] The responses indicated that one-fifth of the pediatricians had difficulties promoting SR due to ambiguity about which specialty or community resources to refer children and families needing help. In developed countries, there are high-quality evidence-based educational intervention programs and community resources integrated into the pediatric primary care setting to support parents on how to best prepare their child for school such as Reach out and Read, Let's Read, Positive Parenting Program, and Head Start.[14,38,39] Unfortunately, there is a lack of clinic-based, culturally tailored, and feasible early childhood educational interventions and parenting models in low and middle-income countries.

There are some limitations to this study. Since participation in the survey was voluntary, a response bias is possible because more pediatricians with a greater interest in the topic may have completed the questionnaire.[40] Because this study is based on self-report, pediatricians may not have fully reported their actual practices. Another limitation is the lack of standardized data collection instruments on the topic of SR, and the study's dependency on a survey without reliability and validity. Nonetheless, the large sample size and being based on a nationally representative sample, which provides the generalizability of our results are the major strengths of our study. The data from our research is significant in identifying and addressing problems in promoting SR within the healthcare system in Türkiye and other countries with similar resources.

In conclusion, pediatricians are the key professional source for promoting SR in children. Given the evidence for the potential long-term implications, our findings suggest a strong need for additional training regarding the roles and responsibilities of pediatricians on SR, along with addressing multiple, modifiable barriers within the healthcare system.

Ethical approval

Ethical approval was obtained from Ankara Bilkent City Hospital Ethics Committee (01.09.2021; E2-21-758).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: PC, TCY, IAS; data collection: PC, TCY, OB, GKE, AU, IAS, DS, TC; analysis and interpretation of results: NOE, PC; draft manuscript preparation: PC, TCY, IAS. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Food and nutrition literacy: a predictor for diet quality and nutrient density among late adolescents

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ABSTRACT

Background. Evidence regarding an individual's food and nutrition literacy (FNL), and its impact on dietary behaviours, could guide the development of more effective interventions. This study sought to examine the association between FNL and its components with diet quality and nutrient density among Iranian senior high-school students.

Methods. In this cross-sectional study, 755 senior high school students were recruited from high schools in Tehran, Iran. FNL was assessed using the Food and Nutrition Literacy Assessment Tool (FNLAT), a self-administered questionnaire which has been locally designed and validated. Dietary assessment was performed by obtaining two 24-hour dietary recalls. Healthy Eating Index-2010 (HEI-2010) and nutrient-rich food index 9.3 (NRF9.3) were calculated to evaluate diet quality. Socioeconomic status, anthropometric measures, and the health status of participants were also assessed.

Results. Higher FNL score was significantly correlated with higher HEI-2010 ($\beta = 0.167$, $p < 0.001$) and NRF9.3 ($\beta = 0.145$, $p < 0.001$) scores. Subgroup analysis indicated that these associations were significant only among males, but not females. Regarding components of FNL, skill dimension of FNL was a stronger predictor for HEI-2010 ($\beta = 0.174$, $p < 0.001$) and NRF9.3 ($\beta = 0.153$, $p < 0.001$) than knowledge ($\beta = 0.083$, $p = 0.054$ for HEI-2010 and $\beta = 0.107$, $p = 0.01$ for NRF9.3).

Conclusions. FNL may be a significant predictor of diet quality and nutrient density among late adolescents. To improve the effectiveness of food and nutrition education, emphasis must be placed on skill development.

Key words: adolescents, diet quality, food literacy, nutrient density, nutrition literacy.

Unhealthy eating habits are known as a major risk factor for non-communicable diseases (NCDs).[1,2] It has been estimated that improving dietary intakes could prevent one in every five deaths, globally.[3] Across the lifespan, unhealthy eating behaviors are highly prevalent among adolescents and youths in both developed and developing countries.[4] In Iran, a developing country, inappropriate dietary practices, including high consumption of unhealthy snacks and junk foods, breakfast skipping, and inadequate intake of whole grains, dairy products, fruits, and vegetables, are very common among youth.[5,6] Poor dietary practices developed during childhood and adolescence

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may persist into adulthood[7,8], deleteriously impacting health in later life.[9]

Concomitant to sociocultural and environmental factors affecting the quality of dietary intakes, personal knowledge and skills about food and nutrition could be an important predictor of food choices.[10,11] Lack of skills and knowledge about food and nutrition such as knowing what foods are made of, how food labels should be interpreted and used, how healthy food can be prepared, how accurate information can be achieved, etc., could be related to poor food choice and lower diet quality.[12] The concept of food and nutrition literacy (FNL) has been developed in order to address such competencies in three levels: functional, interactive, and critical.[13,14] Most of the existing research has focused on nutrition knowledge and its relation to eating behaviors.[10,15] Even nutrition education interventions have mainly addressed knowledge aspects rather than skills; a fact that may explain the relatively low effectiveness of such interventions.[11,16] In the FNL concept, although food and nutrition knowledge represents an essential component, strengthening skills concurrently with knowledge, in particular, has been posited as a more effective approach to promoting healthy and sustainable eating behaviors. Understanding the relationship between FNL (and its components) and dietary intakes could guide the development of more effective strategies. However, as FNL is a recently emerged concept, the number of studies examining the relationship between FNL and eating behaviors are limited.[17-23]

In the, albeit limited, extant literature, it has been suggested that FNL is positively correlated with diet quality and healthy eating behaviors.[17-25] However, in most of these studies, the extent to which each domain of FNL, i.e. knowledge and skills could predict the quality of dietary intakes has not been determined.[19-23] The two available studies that have addressed both skill and knowledge were conducted in children[17] and adults[18], but no evidence is currently available pertinent to adolescents or youth.

We have previously reported low FNL status of Iranian late adolescents[26]; however, the association between FNL status and eating behaviors remained unclear. Considering the gaps in the current knowledge base, this study was conducted to examine the association between food and nutrition literacy, and its component, with diet quality and nutrient density among Iranian senior high-school students.

Material and Methods

The data of the current school-based cross-sectional study was collected in the city of Tehran from November 2017 to April 2018. The participants were 755 senior high-school students, aged 17-18 years, recruited from different socioeconomic districts through multistage cluster randomized sampling method. Being enrolled in senior high-school grade, not following any special diet, and willingness to participate in the study were the inclusion criteria. If a participant did not meet inclusion criteria, he/she would be replaced by another student through random selection. Of the recruited participants, 621 provided complete demographic, dietary intake, and FNL data (Fig. 1).

Food and nutrition literacy

Food and nutrition literacy (FNL) was assessed by Food and Nutrition Literacy Assessment Tool (FNLAT). This self-administered 60-item questionnaire has been developed and validated for Iranian late adolescents and youth.[27] FNLAT includes two main subscales i.e., knowledge and skills. Knowledge is a unidimensional subscale (food and nutrition knowledge), while skill consists of 5 dimensions, including functional skills (by which people can function effectively in everyday situations), interactive skills (interpersonal communication skills related to food and nutrition and seeking food and nutrition information), advocacy (capacity for taking social actions to promote healthy and sustainable food choices), critical

analysis of information (appraising food and nutrition information critically), and food label reading skill.[27] The scores for total FNL and each dimension could range from 0 to 100, with higher scores indicating a higher level of FNL. FNLAT scores <45, >45-60<, and >60 are interpreted as poor, moderate, and adequate level of FNL, respectively.

Dietary intakes

In order to assess dietary intakes, two 24-hour dietary recalls were obtained through in-person interviews with students and complementary phone interview(s) with their mothers or someone who is responsible for food preparation at home. The USDA automated multiple-pass method was used to enhance the accuracy of the collected 24-hour recalls.[28] Trained nutritionists carried out dietary assessment interviews and analysis. For nutrient analysis of the diet, a modified version of Nutritionist IV software in which Iranian foods had been added was used. Under and over reporters were identified according to the method suggested by McCrory et al.[29] and excluded from the analysis (n= 80).

In order to evaluate the quality of the diet, the Healthy Eating Index 2010 (HEI-2010) was calculated using the method explained by the National Cancer Institute.[30] Using this index, reported dietary intakes were compared with the US dietary guidelines. The calculated score could range from 0 to 100, with higher scores representing a healthier diet. Nutrient-Rich Food 9.3 score (NRF9.3) was calculated for the whole diet as a measure of nutrient density. The details of the NRF9.3 calculation have been described by Drewnowski et al.[31] Briefly, the calculation of NRF9.3 is based on 9 nutrients to encourage (or qualifying nutrients), including protein, dietary fiber, vitamin A, vitamin C, vitamin E, calcium, iron, magnesium, potassium; and 3 nutrients to limit (or disqualifying nutrients), including saturated fat, added sugar, and sodium. NRF9.3 is calculated as the sum of the percentage of reference daily values (RDVs) for qualifying nutrients (NR9) minus the sum of the percentage of maximum recommended value (MRVs) for disqualifying nutrients (Lim3). All daily values were calculated per 2000 kcal. The RDVs and MRVs suggested by Drewnowski et al., which are based on different sources i.e., World Health Organization (WHO) and the United States Food and Drug Administration (FDA)[31],were used in the present study.

Covariates

Based on existing evidence[26,32-35], some covariates were considered in the present study. Socioeconomic status was evaluated using a questionnaire in which students were asked about their parents' education level and job position, home appliances and facilities ownership (or type in some cases), and residential house features. A unidimensional SES variable was created from several socioeconomic variables, using principal component analysis (PCA). Participants were also asked about their health status and that of their families. Students' weight was measured using the Seca digital weighing scale to the nearest 0.1 kg, without shoes, and with minimum clothing. Height was measured in a normal standing position of shoulders and without shoes, using a wall-fixed tape measure. WHO AnthroPlus software was applied to calculate body mass index (BMI) for age z-score, and WHO criteria were used to define obesity and overweight.[36]

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving research study participants were approved by the National Nutrition and Food Technology Research Institute (NNFTRI) ethics committee (IR.SBMU.nnftri.Rec.1396.166).

Statistical analysis

Mean ± standard deviation (SD) of quantitative variables and frequency of ordinal/ nominal variables were reported as descriptive statistics. The distribution of categorical variables was compared between FNL levels, using the chi-square test. One-Way ANOVA was applied

to test whether means of normal-distributed quantitative variables were significantly different between FNL levels. Multiple linear regression was used to examine the association between FNL with dependent variables (HEI-2010 and NRF9.3 and their components). The assumptions of linear regression analysis, including homoscedasticity (using scatterplot of the residuals), and lack of multicollinearity (through checking VIF values), and autocorrelations (using Durbin Watson Statistic) were checked before running regression models. SPSS version 21.0 (SPSS Inc., Chicago, Illinois, USA) software was applied to carry out statistical analyses. Statistical significance was accepted at $p < 0.05$.

Results

Demographic characteristics and a description of additional variables of interest (weight status, HEI-2010, and NRF9.3) are summarized in Table I. A total of 755 students participated in this study, of whom, 621 had complete dietary intake (two 24-hour dietary recalls) and FNL data (Fig. 1). After excluding dietary intake mis-reporters, a final sample of 541 students was included in the analysis. In terms of socio-demographic status (SES), we compared included subjects (n = 541) to those who were excluded from the analysis. No significant difference was observed in SES variables (parent education and job position, city district) ($p > 0.05$); however, the distribution of males (n= 70, 32.7%) and females (n= 144, 67.3%) in the excluded subjects was significantly different from those who were included ($P < 0.001$). Post hoc power analysis indicated that the power of linear regression analysis with remaining sample size (n = 541) is still acceptable (for linear regression analysis of FNL predicting HEI-2010, noncentrality parameter $\lambda = 27.82$, critical F = 2.23, power = 0.991; and for linear regression analysis of FNL predicting NRF9.3, noncentrality parameter $\lambda = 29.33$, critical F = 2.23, power = 0.994).

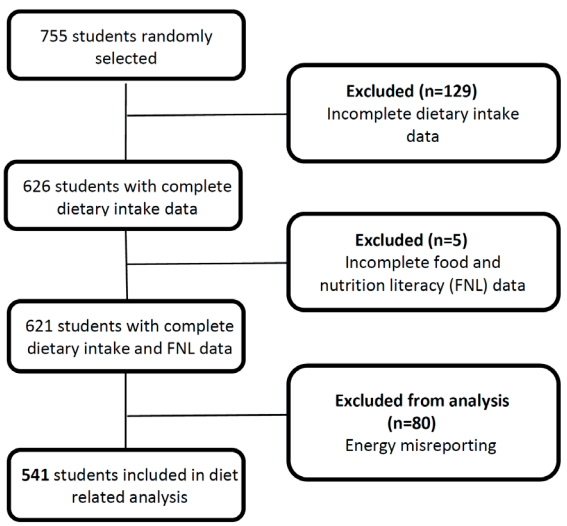

Fig. 1. Flow diagram of participants.

The results of linear regression analysis for the association between FNL and HEI-2010 and NRF9.3 are shown in Table II. A better FNL score was significantly correlated with higher HEI-2010 and NRF9.3 in the crude model. Entering the BMI-for-age z score in model 2 as well as further adjustment for other covariates (gender, SES, and suffering from a nutrition-related disease) did not alter these associations. As presented in Table II, subgroup analysis indicated that the association between FNL and HEI-2010 was statistically significant only among males ($\beta = 0.278$, $p < 0.001$), not females ($\beta = 0.021$, $p = 0.74$). Regarding NRF9.3, a similar result was found, as FNL was significantly related to NRF9.3 only in the males subgroup ($\beta = 0.197$, $p < 0.01$).

The linear regression coefficients for association between the main domains of FNL (knowledge and skills) and skills dimensions (interactive skills, food label reading skill, functional skills, critical analysis of information, and advocacy) with HEI-2010 and NRF9.3 are presented in Table III. As shown in Table III, after adjusting for covariates, HEI-2010 was positively correlated with skill domain ($p < 0.001$), functional skills ($p = 0.01$), interactive skills ($p < 0.001$) and advocacy ($p = 0.001$). Subgroup analysis indicated that these associations were statistically significant among males, but not females. Although food and nutrition knowledge was not a significant predictor for HEI-2010, when regression analysis

Table I. General characteristics of study participants by FNL status.

Characteristics	n	N (%) or Mean ± SD				P value
		Total	Poor FNL	Moderate FNL	Adequate FNL	
Gender	621					0.57 [a]
Male		309 (49.8)	79 (53.7)	158 (49.8)	75 (47.8)	
Female		312 (50.2)	68 (46.3)	159 (50.2)	82 (52.2)	
City district by SES	621					0.50 [a]
High SES		324 (52.2)	74 (50.3)	161 (50.8)	89 (56.7)	
Middle SES		153 (24.6)	33 (22.4)	83 (26.2)	37 (23.6)	
Low SES		144 (23.2)	40 (27.2)	73 (23.0)	31 (19.7)	
Major	621					0.06 [a]
Literature and Humanities		144 (23.0)	38 (25.9)	67 (21.1)	38 (24.2)	
Natural Sciences		215 (34.3)	36 (24.5)	121 (38.2)	56 (35.7)	
Mathematics		267 (42.7)	73 (49.7)	129 (40.7)	63 (40.1)	
Father education	620					0.32 [a]
Illiterate		11 (1.8)	1 (0.7)	6 (1.9)	4 (2.6)	
Under diploma		126 (20.3)	37 (25.2)	61 (19.2)	28 (17.9)	
High school diploma		286 (46.1)	72 (49.0)	142 (44.8)	72 (46.2)	
Associate degree or higher		197 (31.8)	37 (25.2)	108 (34.1)	52 (33.3)	
Maternal education	621					0.78 [a]
Illiterate		15 (2.4)	3 (2.0)	10 (3.2)	2 (1.3)	
Under diploma		130 (20.9)	34 (23.1)	66 (20.8)	30 (19.1)	
High school diploma		316 (50.9)	76 (51.7)	156 (49.2	84 (53.5)	
Associate degree or higher		160 (25.8)	34 (23.1)	85 (26.8)	41 (26.1)	
Weight status	593					0.13 [a]
Normal		337 (56.4)	89 (64.0)	172 (56.2)	73 (49.3)	
Overweight		147 (24.6)	26 (18.7)	76 (24.8)	45 (30.4)	
Obese		114 (19.1)	24 (17.3)	58 (19.0)	30 (20.3)	
Student's age	621	17.82 ± 0.39	17.88 ± 0.45	17.79 ± 0.38	17.82 ± 0.39	0.09 [b]
Paternal age	613	48.62 ± 5.53	48.85 ± 5.90	48.63 ± 5.43	48.28 ± 5.39	0.66 [b]
Maternal age	616	43.18 ± 5.24	43.44 ± 5.43	43.08 ± 5.16	43.16 ± 5.24	0.76 [b]
HEI-2010 score	541	66.56 ± 10.43	64.87 ± 10.31	66.17 ± 10.16	69.16 ± 10.71	**0.003** [b]
NRF9.3	541	404.41 ± 175.4	380.01 ± 160.2	398.64 ± 168.6	442.05 ± 198.5	**0.012** [b]
NR9	541	669.49 ± 151.0	642.20 ± 137.8	666.90 ± 144.0	703.37 ± 172.2	**0.004** [b]
LIM3	541	265.08 ± 62.7	161.06 ± 64.8	268.26 ± 60.3	261.32 ± 65.8	0.447 [b]

[a] Statistical significance was examined using chi-squared test
[b] Statistical significance was examined using one-way ANOVA test
FNL: food and nutrition literacy, HEI: healthy eating index, NRF: nutrient rich food, SD: standard deviation, SES: socio-economic status
NR9, Sum of the percentage of reference daily values (RDVs) for qualifying nutrients
LIM3, Sum of the percentage of maximum recommended value (MRVs) for disqualifying nutrients

was performed by gender, the β coefficient value was significant in males (β = 0.143, p = 0.01). NRF9.3 was significantly correlated with both skill (p < 0.001) and knowledge (p = 0.01) domains of FNL, although the observed association was relatively weaker with the knowledge domain (β = 0.107 vs. β = 0.143 in the skill domain). Among skill dimensions, functional skills (p = 0.04), interactive skills (p = 0.002), and advocacy (p = 0.001) were positively associated with NRF9.3. These skill dimensions were significant predictors of NRF9.3 only in the males subgroup.

Table II. The results of linear regression analysis for FNL predicting diet quality (HEI-2010) and nutrient density (NRF9.3) by gender.

	All			Males			Females		
	β	SE	R^2	β	SE	R^2	β	SE	R^2
HEI-2010									
Model 1	**0.167*** **	0.041	0.028	**0.276*** **	0.052	0.076	0.022	0.064	0.064
Model 2	**0.168*** **	0.041	0.029	**0.275*** **	0.053	0.078	0.030	0.588	0.002
Model 3	**0.167*** **	0.041	0.050	**0.278*** **	0.051	0.147	0.021	0.066	0.003
NRF9.3									
Model 1	**0.168*** **	0.006	0.028	**0.185** **	0.007	0.034	**0.145***	0.009	0.021
Model 2	**0.156*** **	0.007	0.024	**0.188** **	0.009	0.034	0.108	0.011	0.014
Model 3	**0.154*** **	0.007	0.054	**0.197** **	0.009	0.061	0.102	0.011	0.023

Model 1: Crude model
Model 2: Adjusted for BMI for age
Model 3: Adjusted for BMI for age, SES, suffering from nutrition-related disease, gender (only for "All" column).
*** P < 0.001, ** P < 0.01, * P < 0.05
FNL: food and nutrition literacy, HEI: healthy eating index, NRF: nutrient rich food, SES: socio-economic status

The relationship between components of HEI-2010 and NFR 9.3 with total FNL score and two main domains of FNL (knowledge and skill) are presented in Table IV. Among HEI-2010 components, total fruits, whole fruit, greens and beans, seafood and plant proteins, refined grains, and sodium were significantly predicted by total the FNL score and skills score. The association between the "total vegetable" score and total FNL and skills score were statistically significant ($p < 0.05$) but negligible ($\beta < 0.1$). Knowledge score also had a significant but negligible correlation with the score of "whole fruit" ($\beta = 0.089$). Regarding NRF9.3 components, the score of vitamin C ($p = 0.002$), calcium ($p = 0.03$), and potassium ($p < 0.001$) were significantly correlated with total FNL score, but the β value for calcium showed a poor association ($\beta = 0.097$). While the knowledge score had no significant relation with NRF9.3 components, a higher skill score was significantly associated with a higher intake of vitamin C ($p = 0.001$), magnesium ($p = 0.02$), and potassium ($p < 0.001$) scores.

Discussion

The findings of the present study indicated that food and nutrition literacy (FNL) could be a significant predictor of diet quality and nutrient density among late adolescents, especially adolescent males. Similarly, the positive association between Food/nutrition literacy and dietary diversity[17], diet quality[18-20,23], healthy eating behaviors[21,24,25], healthy dietary pattern[22] has been reported in different age groups.

Adolescents and youths who have higher levels of FNL have more information about nutrition and foods; and are more skilled in applying basic food and nutrition knowledge, preparing healthy meals, seeking food and nutrition information, appraising such information (critical analysis skills), and even advocating to address barriers to healthy and sustainable food choices.[37] Although all these competencies can result in healthier food choices, and approaches to develop these competencies should be included in educational programs, the results of the current study indicated that food and nutrition related skills were a stronger predictor for healthy eating behavior than knowledge. In the present study, the knowledge domain of FNL was not associated with the components of HEI-2010 and NRF9.3, whereas higher levels of food and nutrition related skills were significantly associated with a higher intake of fruits (total and whole fruit components), vegetables (green and beans components), seafood and plant proteins, and lower intakes of refined grains and sodium; in addition to a

Table III. The results of linear regression analysis for FNL components predicting diet quality (HEI-2010) and nutrient density (NFR9.3) by gender.

	FNL domains																			
	Knowledge			Skills			Functional			Interactive			Skill dimensions: Advocacy			Analysis of information			Food label reading skills		
	β	SE	R^2	β	SE	R^2	β	SE	R^2	β	SE	R^2	β	SE	R^2	β	SE	R^2	β	SE	R^2
HEI-2010																					
All[a]	0.083	0.038	0.028	0.174***	0.038	0.053	0.103*	0.025	0.033	0.182***	0.024	0.055	0.143**	0.022	0.043	0.046	0.028	0.025	0.032	0.014	0.023
Males[b]	0.143*	0.038	0.091	0.285***	0.048	0.0151	0.201***	0.033	0.110	0.278***	0.029	0.148	0.181**	0.029	0.103	0.015	0.036	0.072	0.061	0.018	0.075
Females[b]	0.011	0.049	0.003	0.036	0.061	0.004	0.005	0.037	0.003	0.047	0.042	0.005	0.077	0.034	0.009	0.087	0.042	0.011	0.00	0.021	0.003
NRF9.3																					
All[a]	0.107*	0.005	0.042	0.153***	0.006	0.054	0.086*	0.004	0.038	0.137**	0.044	0.050	0.138**	0.004	0.050	0.021	0.005	0.031	0.061	0.002	0.034
Males[b]	0.097	0.006	0.031	0.210***	0.008	0.066	0.132*	0.005	0.040	0.207***	0.005	0.066	0.139*	0.005	0.042	0.007	0.006	0.023	0.069	0.003	0.027
Females[b]	0.111	0.009	0.024	0.088	0.011	0.020	0.038	0.006	0.014	0.044	0.007	0.014	0.133*	0.006	0.030	0.051	0.007	0.015	0.041	0.004	0.014

[a]Adjusted for BMI-for-age, suffering from nutrition-related diseases, SES, and gender

[b]Adjusted for BMI-for-age, suffering from nutrition-related diseases, and SES

*** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$

BMI: body mass index, FNL: food and nutrition literacy, HEI: healthy eating index, NRF: nutrient rich food, SES: socio-economic status

higher amount of vitamin C, potassium, and magnesium in the diet. Indeed, the findings of the present study provide further evidence that food/nutrition knowledge alone is not sufficient to establish positive changes in dietary behaviors.[38] This notion should be taken into account by educational program planners and curriculum designers, especially in the context of the Iranian education system which is predominantly focused on knowledge aspects, rather than skill development.[39,40]

The other notable finding of the present study was that FNL was a significant predictor for diet quality and nutrient density among males, but not females. Similar findings have been reported by another study conducted among Iranian adolescents (aged 13-15), where subgroup analysis indicated that the association between nutrition literacy and diet quality (assessed by revised children diet quality index) was significant only among males.[20] Indeed, evidence suggests that the possibility of misreporting in dietary intakes is higher among females than male adolescents.[41] Although we excluded misreporters from the analysis, the method used to identify misreporters is based on comparing reported energy intake with energy requirement. There is the possibility that some people tend to report healthier dietary intakes (than their actual values) meanwhile their reported energy intake may be plausible. Also, the eating behaviors of adolescent females are more likely to be influenced by factors like body image, self-esteem, or self-evaluation than males[42,43], which may overshadow the impact of their FNL level on eating practice. Finally, the limited number of studies comparing this relationship between female and male adolescents[20] makes it difficult to draw a reliable conclusion and explanation in this regard, thereby warranting further research.

In the present study, NRF9.3 was calculated to assess the nutrient density of the diet. To our knowledge, this is the first study that has examined a nutrient density score in relation to FNL. This score can be calculated for individual foods, as well as for the whole diet.[44]

Table IV. Multiple linear regression relationships between FNL (and its domain) and components of HEI-2010 and NFR 9.3.

	Total FNL			Knowledge			Skills		
	β	SE	R^2	β	SE	R^2	β	SE	R^2
HEI-2010 components									
Total fruit	**0.104***	0.007	0.034	0.085	0.005	0.030	**0.101***	0.007	0.034
Whole fruit	**0.110***	0.008	0.038	0.089*	0.005	0.033	**0.108***	0.007	0.037
Total vegetables	0.094*	0.006	0.017	0.041	0.004	0.10	0.097*	0.005	0.015
Greens and beans	**0.0128****	0.008	0.029	0.042	0.006	0.013	**0.132****	0.008	0.030
Seafood and plant proteins	**0.113***	0.008	0.038	0.078	0.006	0.032	**0.108***	0.007	0.037
Refined grains	**0.115***	0.014	0.062	0.043	0.010	0.048	**0.122****	0.013	0.065
Sodium	**0.109***	0.007	0.020	0.060	0.005	0.012	**0.111***	0.006	0.020
NRF components									
NRF vitamin C	**0.140****	0.004	0.048	0.080	0.003	0.035	**0.143****	0.004	0.049
NRF calcium	0.097*	0.001	0.017	0.082	0.001	0.015	0.087	0.001	0.015
NRF potassium	**0.160*****	0.001	0.058	0.075	0.000	0.036	**0.162*****	0.001	0.058
NRF magnesium	0.083	0.001	0.021	0.005	0.001	0.015	**0.100***	0.001	0.025

Adjusted for BMI-for-age, suffering from nutrition-related diseases, SES, and gender
*** P < 0.001, ** P < 0.01, * P < 0.05
BMI: body mass index, FNL: food and nutrition literacy, HEI: healthy eating index, NRF: nutrient rich food, SES: socio-economic status

Among various NRF models, NRF9.3 has indicated the best validation results against HEI-2005[45] and has been reported to be associated with lower all-cause mortality risk.[46] In the present study, FNL and its components (especially in the skill domain) were significant predictors of NRF9.3., suggesting that improving FNL status may lead to consuming a diet rich in qualifying nutrients (e.g., dietary fiber, vitamin A, vitamin C, vitamin E, etc.) and limited in disqualifying nutrients (i.e., saturated fat, added sugar, and sodium) among adolescents and youth; the age group in which high consumption of unhealthy snacks and convenient foods (which are mostly energy-dense, nutrient-poor) are prevalent.[5,6] These findings reemphasize the importance of applying FNL promoting strategies in order to achieve health outcomes among adolescents and youth.

Although we provide a novel addition to the literature of practical relevance, this study had some limitations that are worth noting. The cross-sectional design of the study precludes causal inferences regarding the direction of the observed association between FNL and diet quality. In addition, we selected a representative sample of senior high-school students of Tehran city; however, the studied population is not a nationally representative sample of Iranian adolescents. Therefore, the results may not be generalizable, for example, to younger adolescents or rural communities, highlighting the need for further studies in these populations. In order to enhance the accuracy of the collected 24-hour recalls, we applied the USDA automated multiple-pass method, employed a trained nutritionist, and performed complementary interviews with parents; however, random and systematic errors in self-reported dietary assessment is inevitable.[47]

In conclusion, the results of the current study demonstrated that food and nutrition literacy may build a capacity to adopt healthy eating behaviors in late adolescents, especially among adolescent males. The results also highlighted the importance of focusing on skill development in the context of food and nutrition education, which may be useful in the development of effective intervention strategies.

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Ethical approval

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving research study participants were approved by the National Nutrition and Food Technology Research Institute (NNFTRI) ethical committee (IR.SBMU.nnftri.Rec.1396.166).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: MA, NO, ES, HEZ; data collection: MA, NO, AD, BAE, SS, MM; analysis and interpretation of results: MA, CCTC, SS; draft manuscript preparation: MA, CCTC, NO. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Evaluation of adolescents with heavy menstrual bleeding using the International Society of Thrombosis Haemostasis-Bleeding Assessment Tool and The Pediatric Bleeding Questionnaire scores

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ABSTRACT

Background. Heavy menstrual bleeding (HMB) is a common condition in adolescents. However, bleeding disorders are known to be one of the causes of HMB in adolescent girls, so they should be considered. Simple methods that can be used in primary health care are needed to determine whether patients have bleeding disorders.

The aim of this study was to evaluate the bleeding score of patients admitted with HMB and to determine the diagnostic value of patients who were symptomatic but whose initial hemostatic tests were normal.

Methods. A total of 113 adolescents with HMB and 20 healthy adolescent girls were included in the study. The Pediatric Bleeding Questionnaire (PBQ) and the International Society of Thrombosis Haemostasis-Bleeding Assessment Tool (ISTH-BAT) were used for evaluation.

Results. Overall, approximately 18% (n= 20) of the adolescents in the study were diagnosed with a bleeding disorder. The cut off value for the 'clinically significant bleeding score' was found to be 3.5.

Conclusions. The PBQ and ISTH-BAT can help distinguish a significant bleeding history from an otherwise trivial bleeding and can be included in the algorithm for the primary care of adolescents with HMB with suspected bleeding disorders.

Key words: heavy menstrual bleeding, bleeding disorder, Bleeding Score, Türkiye.

Heavy menstrual bleeding (HMB) is a common condition in adolescent girls, with an incidence ranging from 12.1% to 37%.[1-3] HMB affects patients' quality of life and may lead to symptoms of anemia and iron deficiency. As a result, these patients may require transfusions.[3] A hematology consultation is often requested to evaluate for recurrent iron deficiency anemia and underlying inherited bleeding disorders.

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The main cause of HMB is the immaturity of the hypothalamic-pituitary-ovarian axis. However, bleeding disorders are known to be one of the causes of adolescent HMB, and their complaints should be considered. The number of hemorrhagic symptoms is higher in adolescents when a more severe bleeding phenotype or disorder is present. In the literature, an underlying bleeding disorder has been found in 10% to 62% of patients with HMB.[4-7] The most common inherited bleeding disorder is von Willebrand disease (vWd), whose rate of which is 1% in the normal population but 5-36% in patients with HMB.[8-13]

To determine whether patients have bleeding disorders, simple methods that can be used in primary health care are needed. Standardized bleeding scores have been developed for the diagnosis of bleeding disorders, in which a detailed and accurate bleeding history is obtained. However, there are only a few comprehensive studies in adolescents with HMB. With this study, we aimed to prospectively evaluate the ability of the International Society of Thrombosis Haemostasis - Bleeding Assessment Tool (ISTH-BAT) and Pediatric Bleeding Questionnaire (PBQ) to predict the presence of a previously undiagnosed bleeding disorder in adolescent girls admitted with HMB.

Material and Methods

Patient Study Population

The study was conducted prospectively between October 2020 and March 2021. This study included adolescent girls (age < 18 years) with HMB who were consulted in the Pediatric Hematology Unit of the Dr. Sami Ulus Maternity and Children Research and Training Hospital. The control group (n=20) consisted of adolescent girls admitted to the general pediatric outpatient clinic for preoperative evaluation.

Clinical data, including age at first bleeding event, age at menarche, age at examination, age at diagnosis, time to development of HMB, medical and family history, laboratory test results, final diagnoses and hospitalizations, iron deficiency anemia, need for blood transfusions, and therapeutic modalities, were recorded.

According to the 2018 FIGO diagnostic criteria, HMB was defined as "excessive menstrual blood loss affecting a woman's physical, social, emotional, and/or material quality of life.". Excessive menstrual blood loss was defined as persistent heavy bleeding > 7 days, flooding or gushing sensation, shedding of clots, change of protection every 1-2 hours. Anovulatory bleeding was defined as a menstrual duration < 21 or > 45 days.[14,15]

Patients were divided into 3 groups: HMB with a bleeding disorder (group 1), HMB without a bleeding disorder (group 2), and the healthy control group (group 3).

Informed consent was obtained from the parents/guardians of all patients according to the latest version of the Declaration of Helsinki, and the study was approved by the Ethics Committee of Health Sciences University, Dr. Sami Ulus Maternity and Children Research and Training Hospital (date 10/23/2020, number: E-20/10-011).

Pediatric Bleeding Questionnaire Administration

PBQ and ISTH-BAT were used for assessment.[16-19] The PBQ and ISTH-BAT assess the presence and severity of bleeding symptoms including epistaxis, easy bruising, bleeding from minor wounds, oral cavity bleeding, bleeding after dental or surgical procedures, bleeding from the gastrointestinal tract, menorrhagia, and an 'Other' category that includes venipuncture bleeding, hematuria, and pediatric specific symptoms (umbilical cord hemorrhage, cephalohematoma, and post- circumcision bleeding). The scoring is based on a scale ranging from 0 to 4 in most categories and from -1 to 4 in some categories, with 4 representing the most severe symptoms. Menstrual blood loss was described by a pictorial blood loss assessment chart (PBAC) using the scoring system of Higham et al.[20] A PBAC value of ≥ 100 was used as a cut-off value based on its diagnostic value as described in the original publication.

ISTH-BAT and PBQ were administered face-to-face by a pediatric hematologist to 113 adolescents with HMB and control groups. After obtaining the written consent of the outpatient control persons, bleeding scores were recorded by study doctor and the bleeding history was documented. The time to complete ISTH-BAT and PBQ was 20-25 minutes.

Laboratory Methods and Diagnostic Criteria

The initial evaluation of children with HMB consists of documentation of a detailed personal and family history of bleeding, physical examination, hemoglobin (Hgb), ferritin levels, and an initial hemostasis screening panel, comprising platelet count and morphology, prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen level, clot lysis test and bleeding time (bleeding time was determined by Ivy method). Tests for von Willebrand factor antigen (vWf:Ag), von Willebrand factor ristocetin cofactor activity (vWf:Rco) and FII, FV, FVII, FVIII, FIX, FX, FXI, FXIII levels were included in the screening panel cases with HMB. The bleeding time was used as a test to screen for functional platelet disorders. The Platelet Function Analyzer (PFA-100) test was planned for patients with prolonged bleeding time. The diagnosis of platelet function disorders (PFD) was made using a complete blood count, a blood smear, PFA-100 (including 10 mcg collagen/epinephrine and 50 mcg collagen/adenosine diphosphate as aggregates) and a platelet aggregometer (Chronolog Corporation, Havertown, PA, USA). A PFD was defined as a decrease in platelet aggregation to one or more agonists below 2 standard deviations of the normal laboratory range and/or a prolonged closure time with ADP or epinephrine without exposure to aspirin and other antiplatelet drugs.

In cases of confirmed factor deficiency, the factor assay was repeated within 2–4 weeks. The cut-off values for the diagnosis of clotting factor deficiencies were <0.50 IU/mL for FII, FV, FVII, FVIII, FIX and FX, XIII, <0.70 IU/mL for FXI and <150 mg/mL for fibrinogen.

The diagnosis of vWd depended on low vWf:Ag and vWf:Rco and FVIII:C levels. The lower limits of the normal range for vWf:Ag and vWf:Rco were <0.50 IU/mL.[21] The diagnosis of mild factor deficiency was based on at least two separate measurements of the level of the relevant clotting factor.

Anemia was defined as Hgb <11g/dL and iron deficiency or low ferritin levels were defined as serum ferritin levels ≤ 20 ng/mL. Iron deficiency anemia was defined when both anemia and ferritin levels ≤ 20 ng/mL were present.

Statistical analysis

All analyses were performed using IBM SPSS version 23 (SPSS IL, USA) software. The normality of variables was tested using a D'Agostino-Pearson omnibus normality test. The results are presented as means or medians (25–75% interquartile ranges [IQR]) unless stated otherwise. Comparisons were made between patients based on the diagnosis of bleeding disorders categorical variables were summarized using percentages and ratios and compared using the chi-square test, whereas continuous variables were summarized using appropriate measures of central tendency and dispersion. Parametric tests were used for variables that were distributed normally, while nonparametric tests were utilized for variables without normal distribution. The differences of two independent variables between groups were compared using the Student's t test and for comparison of more than two independent variables, ANOVA was used for the ones with a normal distribution. As a non-parametric test, the Mann-Whitney U test was used for the comparison of two independent variables and for comparison of more than two independent variables, Kruskal-Wallis test was used. The optimal cut off points of the bleeding score for discrimination of case and control groups from each other were evaluated by receiver–operator curve (ROC) analysis calculating the area under the curve (AUC) as giving the maximum sum of sensitivity and specificity (ie, Youden index) for the significant test. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were also calculated at the best cut off point. P value less than 0.05 was considered statistically significant.

Results

A total of 113 adolescents with HMB and 20 healthy adolescents were included in the study, all data were recorded during the study period and full results were collected. The characteristics of the patient and control groups are presented in Table I.

Overall, 18% (n=20) of the adolescents in the study were diagnosed with a bleeding disorder. Our results indicate that vWd is the most common disorder in adolescents with HMB (11.5%), followed by PFD (4.4%) and mild coagulation factor deficiency (FV and FVII, 1.8%). The platelet aggregometer identified platelet defects in 5/113 (4.4%) adolescents. The mean age of the patients was 14.29 ± 1.73 (10.8-17.5) years. The mean age at menarche for the entire cohort was 12.23 ± 1.03 (10-15) years and bleeding disorder evaluation occurred at a median of 2 years from menarche. Of the adolescents, 14% required hospitalization for evaluation and management of HMB. None of the participants had a menstrual duration > 45 days. Forty-seven percent (n = 53) had iron deficiency anemia, 34% (n = 38) had only iron deficiency and overall iron deficiency was observed in 81% (n = 91). In adolescents diagnosed with bleeding disorders, mean hemoglobin (Hb) levels were reported to be similar to those without bleeding disorders (10.7 vs. 10.5). PFA-100 was administered to 8 patients with a prolonged bleeding time. A PFA-100 abnormality was found in 5 of these patients.

Sixteen patients had a history of tooth extraction, one patient twice and one patient with vWD had a history of bleeding after tooth extraction. Eight patients had a history of surgery in the past, one patient twice, and none of them had postoperative bleeding. None of the patients had muscle hematoma, hemarthrosis, or gastrointestinal (GI) system bleeding. The threshold value for ''clinically significant bleeding score'' was determined to be 3.5.

Table I. Characteristics of patient and control groups.

Symptom	Group-1 n=20	Group-2 n=93	Group-3 n=20	p
Age (yr), mean±SD (min-max)	14.77±1.72 (11-17.5)	13.9±1.59 (10.8-17.5)	15.45±1.84 (12-18)	<0.001
Age at menarche (yr), mean±SD (min-max)	12.37±0.74 (11-14)	12.02±1.01 (10-14)	13.10±0.96 (11-15)	<0.001
Hgb (g/dL), Median (IQR)	11.1 (8.2-12.9)	11.1 (8.1-12.6)	13.2 (12.6-13.6)	<0.001
IDA, n (%)	8 (40)	45 (48)	0 (0)	
ID, n (%)	12 (60)	79 (85)	0(0)	
PBAC at study entry, Mean ± SD*	380±145	320±139	61±23	<0.001
ISTH-BAT, Median (IQR)*	4 (4-5)	3 (2.5-3)	0 (0-0.75)	<0.001
PBQ, Median (IQR)*	4 (4-5)	3 (2.5-3)	0 (0-0.75)	<0.001
PBQ without menorrhagia, Median (IQR)	2 (1-3)	0 (0-0.75)	0 (0-0.75)	<0.001
Family history of bleeding, n (%)	N:8 (40)	N:4 (4.3)	N:0 (0)	<0.001
Blood transfusion, n (%)	N:2 (10)	N:14(15)	N:0	0.137
PT (s), mean±SD (min-max)	12.58±1.11 (11-14.5)	12.34±0.88 (9.4-14.4)	12.57±0.95 (10.8-13.8)	0.565
APTT (s), mean±SD (min-max)	27.1±2.51 (23.4-31.7)	25.38±3.06 (17.6-32.3)	26.85±2.02 (23.1-29.7)	0.048

Group 1, HMB with bleeding disorders; Group 2, HMB without bleeding disorders, Group 3, healthy control group.
*There is a statistical difference between the scores of the Groups 1-2 in comparison to Group 3.
APTT: activated partial thromboplastin time, Hgb: hemoglobin, HMB: heavy menstrual bleeding, ID: Iron deficiency, IDA: Iron Deficiency Anemia, IQR: 25–75 % interquartile range, ISTH-BAT: International Society of Thrombosis Haemostasis-Bleeding Assessment Tool, PBAC: pictorial blood loss assessment chart, PBQ: Pediatric Bleeding Questionnaire, PT: prothrombin time.

In our study, we found a bleeding score of 3.85 ± 1.63 (3-10) in HMB patients with existing bleeding disorders, 2.83 ± 1.07 (1-5) in HMB patients without bleeding disorders, and 0.25 ± 0.44 (0 – 1) in the healthy control group. There was no significant difference between the ISTH-BAT and PBQ scores. Without menorrhagia, the bleeding score was 0.95 ± 1.46 (0-6) in Group 1, 0.11 ± 0.35 (0-2) in Group 2, and 0.25 ± 0.44 (0-1) in the healthy control group. Regarding the performance of PBQ as a screening tool to identify bleeding disorders in adolescents with HMB, the ROC curve analysis showed good discrimination with an AUC of 0.90 (95% CI: 0.84; 0 ,96) (Fig. 1). At a threshold of bleeding score (BS)=3.5, the sensitivity was 95%, the specificity was 76.3%, the PPV was 46.3%, and the NPV was 98.6%.

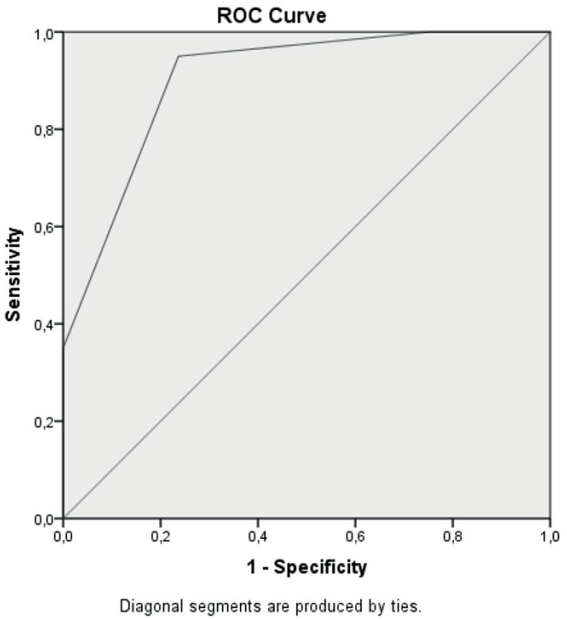

Fig. 1. Receiver operating characteristics (ROC) curve of PBQ to predict the presence of bleeding disorder in patients with HMB at BS=3.5. The ROC curve analysis demonstrated good discriminative ability having an area under the curve (AUC) of 0.90 (95% confidence interval: 0.84-0.96).
BS: bleeding score, HMB: heavy menstrual bleeding, PBQ: Pediatric Bleeding Questionnaire

Discussion

It is usually difficult to assess bleeding disorders in children with HMB. Previously, the use of the ISTH-BAT score in determining bleeding disorders has been studied and previous reports have found that the clinically significant bleeding score is 3-4 overall.[22-24]

In this study, we tried to find the cut-off point in patients with HMB. Our study shows that an ISTH-BAT score of ≥3.5 demonstrates diagnostic accuracy in excluding bleeding disorders in adolescents with HMB. In patients with HMB, an ISTH-BAT score can be used, which could reduce false-positive diagnoses of bleeding disorders and identify those adolescents who are unlikely to benefit from repeat testing.

Iron treatment and transfusion requirements may develop due to iron deficiency anemia caused by HMB. Hematology consultations are often requested to investigate recurrent iron deficiency anemia and underlying hereditary bleeding disorders. 12% of adolescents with HMB require hospitalization. In the literature, the rate of iron deficiency anemia in adolescents with HMB is given as 9-16% and the need for transfusions as 12%.[25-28] In our study, 47% of patients had anemia due to iron deficiency and 14% had at least one transfusion history. Our results were high compared to what has been reported in the literature. The rate of inherited bleeding disorders in adolescent girls with HMB ranges from 10% to 62%.[4-7] The most common inherited bleeding disorders are vWd, which are observed in 1% of the general population and 5-36% in patients with HMB.[8-13] In our study group, the rate of bleeding disorders was 18%. Our results indicate that vWd is the most common condition in adolescents with HMB (11.5%), followed by PFD (4.4%) and mild coagulation factor deficiency (1.8%). In the literature, it is assumed that the prevalence of bleeding disorders is high, but this does not necessarily reflect the general population,

as most subspecialty clinics treat bleeding diathesis more frequently as they are referred more complicated patients. This referral bias probably led to a higher incidence of bleeding disorders in this study compared to primary care settings.

PFD and coagulation factor deficiency are the rarest bleeding disorders seen in women with HMB. The frequency of PFD ranged from 3.2% to 7.0% in studies examining platelet function in women with HMB.[29-31] Our results were similar to those reported in the literature.

In various studies, PBQ has shown a sensitivity of 83% and a specificity of 79% for bleeding disorders in vWd patients.[19] Philipp et al. used an 8-item screening test in 217 adult patients (sensitivity 89%, specificity 72%, haemostatic abnormality was detected in 71% of patients (5% vWd).[32]

However, there are very few studies in adolescents presenting with HMB of ISTH-BAT in the diagnosis of bleeding disorders in HMB was investigated and the clinically significant bleeding score was found in previous reports.[22,23]

The cut-off level for ''clinically significant bleeding score'' was found to be 3.5 in our study, which was relatively lower than in the previous studies. The aim of this study was to assess adolescents with HMB using the pediatric bleeding score and to determine the diagnostic value in those patients who are symptomatic but with normal initial hemostatic tests. We recommend using the ISTH-BAT score because the PBQ and the ISTH-BAT score in our study was similar. In our study, we found a bleeding score of 3.85 ± 1.63 (3-10) in HMB patients with established bleeding disorders, 2.83 ± 1.07 (1-5) in HMB patients without bleeding disorders and 0.25 ± 0.44 (0-1) in the healthy control group. There was no significant difference between the ISTH-BAT and PBQ scores. Without menorrhagia, the bleeding score was 0.95 ± 1.46 (0-6) in group 1, 0.11 ± 0.35 (0-2) in group 2, and 0.25 ± 0.44 (0-1) in healthy controls. In a previous study conducted on vWd, the cut-off level of the pediatric bleeding score was 3.[24] Instead, we identified a score of ≥3.5 as predictive of bleeding disorders in adolescents with HMB. However, our study concludes that our bleeding scores were high due to the selection of a patient group of adolescent girls with HMB. The ISTH-BAT score of ≥3.5 in patients with bleeding disorders was mainly due to the presence of additional bleeding symptoms in HMB. Considering the scores other than HMB, the score was high in the bleeding disorder group, which was comparable to the literature.[19]

The high rates of bleeding disorders could be due to referral bias, as patients needing specialized care were more likely to be referred. This is a limitation of this study.

This study showed that bleeding scores can be used in patients with HMB admitted to primary health care settings and we believe patients with high scores should be referred to the hematologist for further evaluation.

Ethical approval

The study protocol was approved by the Ankara Sami Ulus Training and Research Hospital, and by the University of Health Sciences Ethics Committee (Dated 23.10.2020, number: E-20/10-011). We received written consent from the participants.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: NÖ; data collection: contribution of all authors, analysis and interpretation of results: NÖ; draft manuscript preparation: NÖ, GŞ. All authors reviewed the results and approved the final version of the manuscript.

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The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Evaluation of risk factors, functionalities, and quality of life in patients with pediatric acute arterial ischemic stroke

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ABSTRACT

Background. This study aimed to evaluate the etiology and prognosis of patients followed up for pediatric acute arterial ischemic stroke.

Methods. The clinical characteristics and etiology of patients aged 1 month-18 years who had acute arterial ischemic stroke between January 2010 and December 2020 were retrospectively evaluated. At last follow-up, the patients' functionality (Barthel Index, Functional Independence Measure), quality of life (SF-36 questionnaire), and motor outcomes (Gross Motor Function Classification System) were recorded prospectively/cross-sectionally.

Results. Forty children (25 boys) with a median current age of 112.5 months (range: 3.6-294) were included in the study. The most frequent etiology was prothrombotic disorders, and the most important factor associated with long-term mortality was valvular heart disease. Of the 27 (67.5%) surviving patients, 29.6% had positive motor outcomes and 29.6% were independent according to the Barthel Index. In terms of quality of life, SF-36 scores were highest in the pain scale and lowest in emotional role difficulty.

Conclusions. Determining the etiology and evaluating prognosis are important to plan effective treatment and rehabilitation for pediatric acute arterial ischemic stroke.

Key words: pediatrics, acute arterial ischemic stroke, etiology, risk factors, prognosis.

Arterial ischemic stroke (AIS) accounts for almost half of all strokes in children.[1] Recent epidemiological data show that the annual incidence of pediatric stroke has increased to 1.2-8/100 000 children.[2] The mortality rate of pediatric stroke is 10-40%, with more than half of survivors developing a major neurologic deficit and 15-50% developing epilepsy.[3-5] Cardiac disorders, arteriopathies, and rheumatologic, metabolic, infectious, and genetic diseases are the common risk factors for pediatric stroke.[1,2,4,6-12] In this study, we aimed to evaluate the etiological profiles, functionality, and quality of life, and motor function of pediatric patients followed for acute AIS in a single center.

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Material and Methods

Pediatric patients between the ages of 1 month and 18 years diagnosed with acute AIS were identified by retrospective review of pediatric neurology consultation notes taken between January 2010 and December 2020 at the University of Health Sciences Dr. Sami Ulus Maternity and Children's Training and Research Hospital which is a tertiary care hospital in Ankara, Türkiye. Arterial ischemic stroke was identified as an acute neurological deficit (or isolated seizures in the infants <6 months) with acute infarct(s) corresponding to the arterial regions determined by magnetic resonance imaging (MRI).[2] Excluded from the study were patients whose records could not be accessed, patients with metabolic stroke in the absence of primary cerebrovascular involvement (e.g., organic academia), and patients with transient ischemic attack without infarct, hypotensive watershed injury, reversible hypertensive leukoencephalopathy, or diffuse hypoxic encephalopathy. The patients were evaluated retrospectively in terms of current age, age at the time of diagnosis, sex, parental consanguinity, family history of stroke, initial clinical presentation, laboratory findings, imaging findings (MRI, computed tomography), vascular involvement pattern/trace, electroencephalogram (EEG), comorbidities, treatments, follow-up period, and prognosis.

In treatment, the use of heparin is preferred in patients with high risk of recurrence and patients without bleeding risk. The use of heparin in AIS is indicated in patients with arterial dissection, prothrombotic risk, and embolism risk associated with congenital or acquired heart diseases. The use of warfarin in children is recommended in the presence of congenital or acquired heart disease, arterial dissection, and recurrence despite aspirin therapy.[13]

The patients were divided into three groups according to age at AIS (1 month to <2 years, 2 to <5 years, and ≥5 years) to enable statistical analysis. The following patient data at initial presentation to the hospital were evaluated: complete blood count, serum glucose, serum electrolytes, blood urea nitrogen, creatinine, liver function tests, erythrocyte sedimentation rate, C-reactive protein (CRP), lipid profile, coagulation parameters, metabolic screening, tests related to infectious and vasculitis etiology, electrocardiography, and echocardiography. Additional data included in the analysis were lipoprotein (a), protein C, protein S, fibrinogen, antithrombin III, homocysteine, and factor VII, VIII, IX, XI, XII, XIII levels, active protein C resistance, anti-cardiolipin antibodies, antiphospholipid antibodies, genetic analyses for factor V Leiden, prothrombin G20210A, and methylenetetrahydrofolate reductase (MTHFR) C677T and A1298C mutations, and any other genetic examinations, if performed.

Of these parameters, protein C, protein S, and antithrombin III levels were considered significant if still low at 3 months after AIS. Lipoprotein (a) level higher than 30 mg/dL, homocysteine level higher than 27.9 mmol/L[14], and factor VIII level higher than 150% were accepted as risk factors. Homozygous MTHFR C677T mutation was accepted as a risk factor on its own, while heterozygous MTHFR C677T, and homozygous or heterozygous MTHFR A1298C mutations were considered a risk factor if accompanied by elevated homocysteine. Among the prothrombotic risk factors, we also evaluated dyslipidemia because of its prothrombotic mechanism of action.[1,15-18] Lipid profile risk factors were defined as total cholesterol above 200 mg/dL, low-density lipoprotein (LDL) cholesterol above 130 mg/dL, triglycerides above 100 mg/dL for children aged 0-9 years and above, 130 mg/dL for those aged 10-18 years, and high-density lipoprotein (HDL) cholesterol below 40 mg/dL.[19] Apart

from prothrombotic risk factors, sickle-cell anemia, hemolytic anemia, polycythemia and thrombocytosis were accepted as hematologic risk factors.[11,20] Polycythemia was defined as a hemoglobin level above the 97th percentile for the patient's age.[21]

Mortality status was ascertained from medical records or phone calls. Deaths occurring during the patient's first hospitalization were classified as acute mortality, and all deaths including those that occurred after discharge were defined as long-term mortality.

At last follow-up, surviving patients (n=27) underwent a prospective, cross-sectional prognostic evaluation including functional assessment using the Barthel Index and WeeFIM (Pediatric Functional Independence Measure) and quality of life evaluation using the Short Form 36 (SF-36) quality of life questionnaire.[22-25] Full independence according to the Barthel Index was evaluated as a positive prognosis. Moreover, motor disability was measured using the Gross Motor Function Classification System (GMFCS). A GMFCS score of 1 was accepted as a positive motor outcome. The WeeFIM is an 18-item ordinal instrument that measures functional performance in the motor and cognitive domains. Items are rated from level 1 to 7, where level 1 represents complete dependence, and at level 7 the child completes the task independently without the need for any assistance or device and with no concern regarding safety or taking a prolonged amount of time. Due to the COVID-19 pandemic, assessments of functional ability and quality of life were done by telephone interview. In addition, the presence of aphasia, hemiplegia, recurrence, and epilepsy were recorded at last follow-up.

Statistical methods

Data were analyzed using IBM SPSS version 23. Data distributions were examined with Shapiro-Wilk test. Comparisons of categorical data between groups were made using chi-square and Fisher's exact tests. In comparisons of quantitative data between dichotomous groups, independent two sample t-test was used for normally distributed data and Mann-Whitney U test for non-normally distributed data. Risk factors associated with mortality were examined using binary logistic regression analysis. Backward: Wald model was used to include independent risk factors in the multivariate model. Results were presented as mean, standard deviation, median, and range for quantitative data and as frequency and percentage for categorical data. Statistical significance was accepted at the $p<0.05$ level.

Ethical approval

Ethics committee approval was obtained for the study (date: 07 April 2021, protocol number: E-21/04-143, decision number: 2020-KAEK-141/147, University of Health Sciences, Dr. Sami Ulus Training and Research Hospital). All procedures were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from the parents or guardians of the patients in the prospective part of the study and assent was obtained from the patients themselves when appropriate.

Results

A total of 40 children were included in the study, 25 of whom were male. The most common presenting symptom was seizure. Selected demographic and clinical characteristics of the patients are summarized in Table I.

Multiple risk factors were present in 85% of the patients, and the most frequent etiologic risk factor was prothrombic factors, seen in 67.5% patients. The most common prothrombotic factor in our patients was low HDL cholesterol

(n=14, 35%), followed by high triglycerides (n=11, 27.5%), presence of lupus anticoagulant (n=7, 17.5%), homozygous MTHFR C677T mutation (n=4, 10%), heterozygous factor V Leiden mutation (n=3, 7.5%), high total cholesterol (n=3, 7.5%), high lipoprotein (a) (n=2, 5%), high factor VIII level (n=2, 5%), high LDL cholesterol (n=2, 5%), protein C deficiency (n=1, 2.5%), protein S deficiency (n=1, 2.5%), anti-cardiolipin IgG/IgM positivity (n=1, 2.5% for each), anti-phospholipid IgG positivity (n=1, 2.5%), heterozygous prothrombin G20210A mutation (n=1, 2.5%), and presence of activated protein C resistance (n=1, 2.5%).

Table I. Patient demographics and clinical characteristics (n=40).

Current age (months), mean±SD, median (range)	116.4 ± 72.8, 112.5 (3.6-294)
Age at initial presentation (months), mean±SD, median (range)	69.4 ± 62.1, 45 (1.2-204.7)
Sex (male), n (%)	25 (62.5)
Parental consanguinity, n (%)	18 (45)
Family history of stroke, n (%)	6 (15)
Risk factors, n (%)	
Prothrombotic disorders	27 (67.5)
Cardiac disorders	26 (65)
Infections	13 (32.5)
Hematologic disorders	12 (30)
Arteriopathy/rheumatologic diseases	5 (12.5)
Genetic diseases	3 (7.5)
Metabolic diseases	1 (2.5)
Multiple risk factors	34 (85)
Presenting symptoms, n (%)	
Seizure	17 (42.5)
Motor deficit/weakness	10 (25)
Sensory abnormalities*	1 (2.5)
Change in consciousness	3 (7.5)
Headache	1 (2.5)
Ataxia	2 (5)
Chorea	2 (5)
Ocular motility disorder**	2 (5)
Diplopia	2 (5)
Treatment, n (%)	
Heparin	Initial: 5 (12.5)
Low molecular weight heparin	Initial: 20 (50), Ongoing: 21 (52.5)
Aspirin	Initial: 8 (20), Ongoing: 12 (30)
Warfarin	Initial: 1 (2.5)
Others	Initial: 6 (15), Ongoing: 7 (17.5)
Outcomes, n (%)	
Aphasia	1 (2.5)
Hemiplegia	16 (40)
Development of epilepsy	24 (60)
Recurrence	3 (7.5)
Acute/Long-term (overall) mortality	6 (15) / 13 (32.5)

*Numbness in the right leg and tongue, **Outward deviation of the left eye in one patient and strabismus in another patient

Initial treatment consisted of heparin in five patients (12.5%), low molecular weight heparin (LMWH) in 20 patients (50%), aspirin in eight patients (20%), and warfarin in one patient (2.5%) (Table I). Heparin was used in five patients, most of whom had multiple risk factors (predominantly cardiac; metabolic in one patient), due to suspicion of high recurrence risk. Warfarin was used as the initial treatment in one patient who was followed for cardiac disorder and continued with LMWH during follow-up.

MTHFR polymorphisms without hyperhomocysteinemia are not associated with cerebral stroke. Homocysteine data were available for 16 of the 17 patients with MTHFR polymorphisms. In these 16 patients, the mean homocysteine level was 8.7±2.8 mmol/L (median: 8.7, range: 4-14.6). Homozygous MTHFR C677T mutation was a risk factor in only four patients (10%). The MTHFR polymorphisms detected in the other patients were not considered significant risk factors because their homocysteine values were within normal limits.

The patients' mean hemoglobin level was 12.3±2.5 g/dL (median: 12, range: 7.9-18.2) and 17.5% of the children had polycythemia.

Anterior circulation AIS was present in 45% of the patients, posterior circulation AIS in 32.5% of the patients, and both anterior and posterior circulation AIS were present in 22.5% of the patients. There was basal ganglion infarct in 32.5% of the children, thalamic infarct in 20%, cerebellar infarct in 17.5%, and brain stem infarct in 15% of the children. Ischemic involvement of multiple lobes was present in 16 of the 21 patients with cortical involvement. Five percent of the patients also had hydrocephaly.

Stroke recurred in three patients, all of whom had multiple risk factors. One of these patients had phenylketonuria, homozygous MTHFR C677T mutation, high total and LDL cholesterol, and lupus anticoagulant positivity as risk factors, and recurrence was observed despite receiving heparin and LMWH after the first stroke. The second patient's risk factors included moyamoya disease, chronic hepatitis B virus infection, left ventricular hypertrophy, high total and LDL cholesterol, low HDL cholesterol, and recurrence occurred despite receiving aspirin therapy. In the third patient, risk factors included cardiac disorder, anti-rubella IgM and IgG positivity, anti-hepatitis A virus IgM and IgG positivity, and recurrence was observed despite receiving heparin and LMWH therapy.

Seizure was the initial symptom in 15 (62.5%) of the 24 patients who developed epilepsy.

The mean follow-up period of the patients was 13 months (range: 0.1-108.0). The results of the prognostic assessment of functionality (Barthel Index, WeeFIM), quality of life (SF-36), and motor outcomes (GMFCS) in the 27 surviving patients are shown in Table II. It was determined that eight patients (29.6%) were fully independent (positive prognosis) according to the Barthel Index and eight patients (29.6%) had a GMFCS score of 1 (positive motor outcome).

When quality of life was evaluated according to risk factors, scores for physical role difficulty and emotional role difficulty were higher in patients with arteriopathy/rheumatologic disease compared to those without, and lower in patients with hematologic risk factors compared to those without. In addition, quality of life scores in the psychological well-being domain were lower in patients with hematologic risk factors and higher in patients with genetic risk factors ($p<0.05$).

During follow-up, six patients (15%) died in the acute period and another seven died after the acute period, for a long-term mortality rate of 32.5%. Table III includes a summary of the factors associated with long-term mortality/survival among our patients.

Factors associated with long-term mortality were further analyzed by binary logistic regression analysis using univariate and multivariate models (Table IV). The multivariate model was created with the risk factors of valvular heart disease, follow-up period, and white blood count. When the multivariate model results were examined, the most important finding was that the mortality risk was 268 times higher in patients with valvular heart disease.

Table II. Prognostic assessment of functionality, quality of life, and motor outcomes (n=27).

Functionality – Barthel Index		
	n (%)	
Fully independent	8 (29.6)	Positive prognosis
Lowly dependent	1 (3.7)	Prognosis not positive
Moderately dependent	9 (33.3)	
Highly dependent	7 (25.9)	
Fully dependent	2 (7.4)	
	Mean ± standard deviation	
Barthel Index	68.0 ± 28.9	
Functionality – WeeFIM		
	Mean ± standard deviation	
Motor	66.0±23.3	
Cognitive	28.6±8.4	
Total	94.5±29.8	
Self-care	28.2±11.5	
Sphincter control	11.2±3.6	
Transfers	16.0±5.8	
Locomotion	10.6±4.0	
Communication	11.7±3.4	
Social interaction	16.9±5.1	
Quality of Life – SF-36		
	Mean ± standard deviation	
Physical functioning	49.1±39.1	
Physical role difficulty	37.5±48.6	
Pain	83.6±27.5	
General health perception	38.6±19.7	
Energy/vitality	43.6±17.6	
Social functioning	63.1±31.5	
Emotional role difficulty	36.4±49.2	
Psychological well-being	53.3±10.9	
Motor Outcomes – GMFCS		
	n (%)	
1	8 (29.6)	Positive
2	12 (44.4)	Not positive
3	2 (7.4)	
4	3 (11.1)	
5	2 (7.4)	

GMFCS: gross motor function classification system, SF-36: short form 36, WeeFIM: pediatric functional independence measure

Table III. Statistically significant factors associated with long-term mortality.

		Mortality (n=13)	Survival (n=27)	P
Age range of 2-<5 years	%	46.2	3.7	<0.001
Consanguineous marriage		76.9	29.6	0.005
Presence of ventricular septal defect		38.5	7.4	0.027
Presence of cardiomyopathy		23.1	0	0.029
Valvular heart disease		69.2	29.6	0.018
Presence of lupus anticoagulant		30.8	11.1	0.019
Elevated aspartate aminotransferase		53.8	22.2	0.043
Elevated alanine aminotransferase		30.8	0	0.010
Sodium abnormality		53.8	11.1	0.011
Hypocalcemia		23.1	0	0.029
Elevated C-reactive protein		76.9	33.3	0.034
Follow-up period <6 months		69.2	3.7	0.001
White cell count		15313±6289	10075±2916	0.012
Absolute neutrophil count	/mm^3, mean±SD	10006±5716	5865±3125	0.022
Platelet count		269153±231469	337666±128101	0.039
Pyruvate	mg/L, mean±SD	3.7±0.2	1.0±0.6	0.031
D-dimer	ng/mL, mean±SD	5835.1±8575.5	870.4±1103.0	0.004

Presented as percentages unless indicated otherwise. SD: standard deviation

Table IV. Logistic regression analysis of factors associated with long-term mortality.

	Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P
Age range (1 month-<2 years)				
2-<5 years	2 (0.09–44.35)	0.661		
>5 years	0.053 (0.004–0.648)	0.021		
Consanguinity (no)	7.917 (1.711–36.633)	0.008		
Absence of VSD	7.812 (1.262–48.356)	0.027		
Absence of valvular heart disease	5.344 (1.268–22.523)	0.022	268.204 (1.21–59441.503)	0.042
Normal sodium	8 (1.537–41.637)	0.013		
Normal CRP	6.296 (1.374–28.855)	0.018		
AST	1.025 (0.999–1.053)	0.059		
ALT	1.05 (0.994–1.111)	0.083		
Sodium level	1.037 (0.888–1.21)	0.648		
CRP level	1.091 (0.993–1.198)	0.07		
Follow-up period	0.929 (0.876–0.986)	0.016	0.906 (0.824–0.997)	0.043
Calcium	0.104 (0.021–0.513)	0.005		
White cell count	1.0003 (1.00007–1.0005)	0.007	1.001 (1–1.001)	0.034

ALT: alanine aminotransferase, AST: aspartate aminotransferase, CRP: C-reactive protein, VSD: ventricular septal defect

Discussion

Pediatric AIS is a life-threatening condition that also causes persistent motor deficits in most survivors and is often accompanied by epileptic, cognitive, or behavioral abnormalities.[3,12,26] In this study, 40 patients with pediatric AIS followed in a major tertiary referral children's hospital were retrospectively evaluated in terms of etiology and clinical characteristics

and prospectively/cross-sectionally evaluated in terms of prognosis (functionality, quality of life, motor outcomes, recurrence, epilepsy development, and mortality). Most (85%) of the patients had more than one risk factor, with the most common etiologic risk factor being prothrombic factors (67.5%). At last examination, 40% of the patients had hemiplegia, 60% had epilepsy, and 7.5% had a recurrence. Acute and long-term mortality rates were 15% and 32.5%, respectively.

Etiological risk factors for stroke vary between studies. Similar to our findings, prothrombotic risk factors were present in 63% of pediatric cases in another study.[27] Prothrombotic disorders, infections, and arteriopathy have been reported as the most frequent risk factors for pediatric stroke in various studies.[6,10,12,28,29] deVeber et al.[2] determined that arteriopathy unrelated to infection was the most important risk factor for pediatric stroke (49%), followed by cardiac disorders (28%). Central nervous system infection was a risk factor in only 3% of the AIS cases in their series.[2] In another study examining pediatric AIS cases, the most common risk factor was heart disease (17%), followed by head trauma (13%), rheumatologic disorders (7.5%), meningitis, and encephalitis (4%).[30] Developments in etiological studies have made it possible to better define risk factors. In our study, we determined that prothrombic risk factors were most common, followed by cardiac disorders, infections, hematologic causes, arteriopathy/rheumatologic, genetic, and metabolic diseases. Prothrombotic risk factors were more common in the etiology of stroke in our study than that described in the literature. However, our results are consistent with the literature in identifying prothrombotic risk factors and congenital heart diseases as common risk factors for AIS.[6,10,12,28-30] In addition, considering the negative impact of cardiac risk factors on mortality, we suggest that more studies are needed on the prevention and treatment of AIS in patients with prothrombotic and/or cardiac risk factors.

Our study provides important data on the etiology and prognosis of pediatric AIS. Defining lipid profile changes as a definite prothrombotic risk factor in our study may have contributed to prothrombotic risk factors emerging as the most common etiology. In our patients, high cholesterol level in three patients (7.5%), high triglycerides in 11 (27.5%), high LDL cholesterol in two (5%), and low HDL cholesterol in 14 patients (35%) were identified as risk factors. Lipid profile abnormality was detected in 17 (43%) of our patients. Our results support recent studies emphasizing that dyslipidemia and hypertriglyceridemia are more common in pediatric AIS patients.[31]

More than two-thirds of the patients in our study had multiple risk factors, which was previously reported to be a predictor of stroke recurrence.[5] In the literature, a 7-14% risk of recurrence has been reported for childhood stroke, with rates of recurrence related to a number of causes, the most common of which are heart disease, moyamoya disease and genetic thrombophilia.[5,28,32] All three of our patients with stroke recurrence were found to have more than one risk factor.

It was reported that children who have an acute seizure during stroke or within 24 hours after hospitalization have a higher likelihood of developing epilepsy than children without seizure at the time of stroke.[33,34] Similarly, most (88.2%) of the 17 patients who presented with seizure later developed epilepsy according to the 2014 practical clinical definition of epilepsy of the International League Against Epilepsy.[35] In our study, of the 29 patients with EEG data obtained at initial presentation, five (12.5%) had focal epileptic activity and nine (22.5%) had abnormal background activity. Of the nine patients with background abnormality, slowing of background activity was noted in six (67%), background asymmetry in two (22%), and voltage suppression in one patient (11%). However, long-term video EEG monitoring was not technically possible for every patient, which is a limitation of our study in terms of

the diagnosis of non-convulsive seizures/status epilepticus.

Stroke-related mortality rates between 1-32% have been reported in previous series.[2-4,10,36] In our study, the mortality rate was 15% in the acute period and 32.5% in the long term. The AIS-related acute mortality rate in our study is consistent with the studies in the literature, which have reported pediatric AIS-related in-hospital mortality rates of 14-16.5%.[37-39] Important factors associated with long-term mortality in our patients were parental consanguinity, cardiac disorders, liver function test abnormalities, electrolyte imbalance, high CRP, pyruvate, and D-dimer levels, and young age. In multivariate analysis, valvular heart disease was found to be associated with a 268 times higher risk of death. These data support the literature data pointing to congenital heart disease as the most important risk factor affecting the long-term mortality of pediatric AIS.[38,40-42] In follow-up studies of Canadian stroke patients with an average follow-up period of three years, deVeber et al.[2,3] reported 5% stroke-related mortality and neurologic deficits in 72% of patients (>50% mild). In our study, the rate of stroke-related mortality was 15% in the acute period and 32.5% in the long term, and at last follow-up it was determined that 40% of the patients had hemiplegia, 60% had epilepsy, and 7.5% had stroke recurrence.

Most studies on childhood stroke have shown that neurological deficits occur in 50-85% of survivors.[3,43] In our study, a positive motor outcome according to the GMFCS and full independence according to Barthel Index was achieved in approximately 30% of surviving patients over long-term follow-up (median of 48 months). According to functional assessment using the modified Rankin scale, 56% of children and 55% of young adults were reported to have acceptable functional outcomes after a median follow-up period of 6.9 years.[44] The long-term outcomes of acquired brain disease are known to be better in children than adults because of the plasticity of the brain. However, Simonetti et al.[44] compared the long-term clinical outcomes of stroke in patients younger than 16 years of age and young adult patients (aged 16-44 years) but detected no significant difference in long-term functional outcomes in terms of disability, mortality, or recurrence rates. We observed that 46.2% of the patients who died after the acute period had AIS between the ages of two and five years, while 92.6% of surviving patients had AIS after the age of five years ($p<0.001$). In our study, this supports the view that having a stroke after the age of five is a good prognostic indicator. Another study shows that having a stroke between the ages of 15 and 19 years is associated with higher mortality risk.[45]

It was reported in a prospective observational study on pediatric AIS that according to assessment with the Pediatric Stroke Outcome Measure (PSOM), 61% of children in the study group had an emotional-motor deficiency, 24% had a cognitive and behavioral deficit, 15% had a language production disorder, and 6% had a difficulty understanding language.[10] Felling et al.[46] evaluated data from the International Pediatric Stroke Study and determined that 24.7% of 413 children had moderate to severe deficits according to PSOM scores at 2-year follow-up.The mean WeeFIM total score of our patients was 94.5, the mean motor component score was 66.0, and the mean cognitive component score was 28.6. In a study of 18 patients with childhood stroke (13 of which were ischemic) admitted to a pediatric rehabilitation unit on mean post-stroke day 688, the mean total WeeFIM score was 74.9 at discharge from the unit (mean 55 days after admission).[47] When compared with the literature, functional outcomes of our patients were better according to their follow-up WeeFIM scores. The difference in the etiologic and demographic profiles of the patients, and different clinicians conducting the evaluation at follow up may be possible factors accounting for the outcomes. When we evaluated our patient group within itself according to risk factors, median

WeeFIM scores in the communication domain differed significantly based on the presence of arteriopathy/rheumatologic disease. No other differences in WeeFIM scores were detected in association with the other risk factors.

When quality of life was assessed using the SF-36, we observed that the patients' highest mean score was in the pain scale and the lowest score was in emotional role difficulty. In our review of the literature, we found no previous study using the SF-36 to assess quality of life in pediatric stroke. However, we conducted this evaluation because there is a study on adults in our country which defined the normative SF-36 scores of the regional population.[48] Our results suggest that childhood stroke has important negative effects on emotional development and that children should be supported emotionally after AIS.

The strength of our study is that we evaluated patients with pediatric AIS followed using a detailed multidisciplinary approach in a major tertiary referral children's hospital over a period of 11 years. However, a limitation of our study is that it included a relatively small sample because it was based on data from a single center.

In summary, the most frequent etiology of pediatric AIS in our study was prothrombotic risk factors. Mortality rates were 15% in the acute period and 32.5% in the long term. The most important factor associated with long-term mortality was the presence of valvular heart disease. When the survivors were evaluated, nearly 30% were independent or had positive motor outcomes and 60% had epilepsy. We conclude that determining the etiology and evaluating prognosis are important to plan effective treatment and rehabilitation for pediatric AIS.

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Ethical approval

The ethics committee of University of Health Sciences, Dr. Sami Ulus Training and Research Hospital approved this study (date: 07.04.2021, protocol number: E-21/04-143, decision number:2020-KAEK-141/147).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: FMAÖ, ÜÖ, AF, UAÖ, MK, FGS, BD, DY; data collection: FMAÖ, ÜÖ, AF, UAÖ, MK, FGS, BD, DY; analysis and interpretation of results: FMAÖ, ÜÖ, AF, UAÖ, MK, FGS, BD, DY; draft manuscript preparation: FMAÖ, ÜÖ, AF, UAÖ, MK, FGS, BD, DY. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Case Report

The expectant management of a rare neonatal disease: transient neonatal myasthenia gravis

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ABSTRACT

Background. Transient neonatal myasthenia gravis (TNMG) is an acquired disease which occurs in 10 to 20% of infants born to a mother with myasthenia gravis. Even though it is a self-limiting disorder, it may potentially be life-threatening if prompt diagnosis is not made, and expedient supportive respiratory management is not initiated when required.

Case. Here we describe three infants with TNMG. Two of them developed symptoms of TNMG within 24 hours of life, but one developed symptoms at 43 hours of life. One of the patients had an atypical form of TNMG with contracture and hypotonia. The other two infants survived a typical form of TNMG with hypotonia and poor sucking. All cases resolved spontaneously by one to two weeks of life with conservative management.

Conclusions. Infants born to mothers with myasthenia gravis need to be monitored closely for symptoms of TNMG for the first 48 to 72 hours of life. However, the majority of infants with TNMG traverse a benign course and resolve spontaneously with expectant care.

Key words: transient, neonatal myasthenia gravis, acetylcholine receptor antibodies.

Transient neonatal myasthenia gravis (TNMG) is an acquired disease which occurs in 10 to 20% of infants born to a mother with myasthenia gravis.[1-3] Transient neonatal myasthenia gravis occurs as a result of the passive transfer of maternal antibodies affecting the fetus' synaptic transmission at the motor end plate. It is characterized by abnormal muscle fatigability. Even though a normally self-limited disorder, TNMG may be potentially life-threatening if this condition is not recognized when prompt supportive respiratory management may be required.

Here we describe three infants with TNMG. Two of them developed symptoms of TNMG within 24 hours of life, but one developed symptoms at 43 hours of life. One of the patients had an atypical form of TNMG with contractures and hypotonia. In contrast, the other two infants survived a typical form of TNMG, with hypotonia and poor sucking. All cases resolved spontaneously within one to two weeks of life with conservative management. Informed consents were obtained from the respective families for the photos and write-up about these cases.

Case Report

Case 1 was a baby girl who was born at 39 weeks of gestation via spontaneous vertex delivery. She was noted to be small for gestational age, with a birth weight of 2320 grams. She was the second child born to a 25-year-old mother diagnosed with myasthenia gravis (MG) diagnosed at the age of 23, eight months after delivering her first child, when she presented with ptosis and difficulty in swallowing.

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The mother's blood for was positive acetylcholine receptor antibody. She had developed three episodes of myasthenia crisis two months before she conceived this baby and was on oral pyridostigmine 60 mg four times daily and oral azathioprine 125 mg daily. She was offered a thymectomy, which was postponed because of the pregnancy. Otherwise, there was no history of polyhydramnios during pregnancy.

Although this baby was vigorous at birth, she was noted to have poor sucking and a weak cry shortly after. Examination revealed facial diplegia (Fig. 1), poor sucking, and hypotonia of all four limbs with fixed flexion deformity involving both elbows (Fig. 2) and knees. A diagnosis of TNMG was made, and her blood investigation later showed that acetylcholine receptor (AChR) antibodies were 30-fold above normal (8.4 nmol/L [Normal level: < 0.25 nmol/L]).

Given her symptoms and maternal intrapartum history of prolonged rupture of membranes which occurred 24 hours prior to delivery, she was treated for presumed sepsis with intravenous penicillin and gentamicin. She subsequently required respiratory support due to recurrent apnoea, which resolved after stopping the aminoglycoside. She was on tube feeding for two weeks as her sucking was poor. Her symptoms improved gradually after the second week of life with good sucking and improved muscle tone. She was started on physiotherapy for her contracture during her stay in the ward. She was discharged well, and on subsequent follow-up visits the contractures at both elbows and knees were less severe.

Case 2 is the younger sibling of Case 1, and was born one year later via elective Caesarean section at 38 weeks. Throughout the pregnancy, her mother was in a remission state while on oral prednisolone 15 mg and oral azathioprine 125 mg daily. She was born small for gestational age, birth weight of 2470 gr. She developed respiratory distress shortly after birth, requiring non-invasive ventilation for seven hours and was subsequently stable on room air. At 30 hours of life, she developed bilateral ptosis, poor sucking, hypotonia (Fig. 3) and a weak cry. Blood investigation also showed elevated AChR antibodies, 13-fold above normal (3.45

Fig. 1. Case 1 with facial diplegia, hypotonia and had poor sucking.

Fig. 2. Case 1 showing fixed flexion deformity of both elbows.

Fig. 3. Case 2 with bilateral ptosis, facial diplegia, hypotonia and poor sucking.

nmol/L [Normal level: < 0.25 nmol/L]). Despite a lower antibody level, this younger sibling's presentation was more acute. She was tube fed for the first four days of life. Sucking improved subsequently with normal muscle tone. She was discharged earlier than her older sibling, on day six of life.

Case 3 was a baby girl born via elective Caesarean section at 38 weeks. She was the second child to a mother aged 35 with ocular myasthenia gravis, diagnosed at 28 years of age. The mother had been on oral pyridostigmine 60 mg four times daily throughout pregnancy and remained in remission. This baby was also vigorous at birth, like the previous two cases, but developed respiratory distress soon after in the postnatal ward at 43 hours of life. Upon examination, she was noted to have poor sucking and hypotonia. She was on respiratory support with a high-flow nasal cannula for one day. Blood investigation showed elevated AChR antibodies, 30-fold above normal (8.5 nmol/L [Normal level: < 0.25 nmol/L]). She received syringe feeding for three days until her sucking had improved. She was discharged well on day five of life.

Discussion

The prevalence of MG occurring in the general population is 77.7 cases per million persons.[4] The infant born to a mother with MG is at risk of having TNMG with an incidence of 10 to 20%.[1-3] However, the risk of TNMG in a sibling, is significantly higher in subsequent pregnancies, as described in our cases.[2]

Infants born to women with MG may have a transient neonatal myasthenic syndrome because of placentally transferred maternal anti-AChR or anti-muscle-specific receptor tyrosine kinase (MuSKR) antibodies.[5] Circulating maternal autoimmune antibodies in fetal circulation are thought to block the postsynaptic neuromuscular junction.[6] The pathogenic role of these antibodies is still unclear because there was no correlation between maternal disease severity or maternal antibody titres with neonatal myasthenia. However, specificity of antibodies, in that, a higher ratio of anti-fetal to anti-adult AChR antibodies in the myasthenic mother may predispose to the occurrence of neonatal MG, and more severe or persistent myopathic features such as, arthrogryposis.[3]

There are two clinical forms of TNMG: the typical presentation, which is more common, with an incidence rate of approximately 71% and, the atypical form in about a third (29%).[1] The typical form commonly develops symptoms more rapidly, as in Case 2 and 3, that include poor sucking and swallowing, weak cry, facial diplegia and ptosis, ophthalmoparesis, generalized hypotonia and respiratory distress. Some infants develop severe respiratory distress requiring assisted mechanical ventilation. In a systematic review by Kochhar et al.[7], only one out of 147 patients required intubation. In two-

thirds of infants, symptoms develop within the first few hours after birth, while most infants (78%) would have developed symptoms by the first 24 hours of life. Cases presenting with symptoms beyond 72 hours of life are extremely rare.[1]

In contrast, the atypical form of TNMG, such as Case 1, may present with clinical features that include multiple joint contractures and arthrogryposis, which gradually improve with time. It may also be associated with pulmonary hypoplasia, likely attributed to impaired chest wall development or reduced fetal breathing efforts.[8] Fetal or early neonatal death is more common in this form.[1,5,9] The risk of this condition continues for subsequent births.[8]

The presence of high concentrations of anti-AChR or anti-MuSKR antibodies in the plasma of affected newborns, along with the maternal clinical history of MG, is pathognomonic of TNMG.[5] Other investigations for TNMG, but less commonly employed, include pharmacologic testing with the administration of acetylcholinesterase agents (e.g., neostigmine methylsulfate or edrophonium chloride) which transiently correct the neuromuscular transmission defect. Repetitive nerve stimulation is rarely done as a test.[1]

Certain drugs, such as aminoglycoside, may potentiate myasthenia and, therefore, should be avoided. The worsening of symptoms is probably due to this drug competitively inhibiting the release of acetylcholine from the presynaptic membrane.[10]

All three patients recovered over the first or two weeks of life. An affected infant would regain normal muscle strength after the circulating maternal antibodies disappear from the body. Complete recovery is expected in less than two months in 90% of infants, and the remaining 10% should fully recover by four months of age without residual neurological impairment, especially in the typical form.[1]

In patients with mild symptoms, giving frequent small oral feedings and continuous close monitoring during the first week of life is recommended before it is safe to discharge. For patients with moderate to severe symptoms, and to accelerate success in oral feeding, neostigmine methylsulfate may be an option but is rarely sought after. Neostigmine is administered intramuscularly or subcutaneously (0.05 mg/kg) or orally (0.5 mg/kg), up to a half-hour before feeding.[1] However, neostigmine administration may cause adverse side effects such as respiratory depression, cardiac arrhythmia and gastrointestinal disturbance. These side effects may be difficult to distinguish in a neonate. In the majority of infants, the condition resolves spontaneously.[11] Without pharmacological intervention, symptoms will gradually resolve in one to four weeks.[12]

Although plasmapheresis, intravenous immunoglobulin (IVIG), and corticosteroids are all efficacious in treating MG in older children and adults, these are rarely needed and only necessary for the management of severely affected neonates for rapid removal of circulating antibodies in life-threatening situations.[2] Our cases did not need IVIG as they were mild, transient and the potentially life-threatening respiratory depression was promptly recognised and ameliorated with non-invasive ventilatory support. IVIG is a high-cost drug with immune-modulating effects that may potentially pose long-term side effects on the developing immune system. Also, the usage of IVIG in treating TNMG has variable outcomes, and future studies on IVIG and exchange transfusion in severe TNMG are needed.[13-15]

As a conclusion, an infant born to a mother with MG needs to be observed for symptoms of TNMG at least over the first 48 to 72 hours of life, regardless of the severity of maternal MG status. However, as in the presented cases, it is emphasised that most infants with TNMG resolve spontaneously with expectant care.

The atypical form of TNMG may be more serious, affecting the limb musculature and possibly lung development. These infants are at risk of intrauterine or early neonatal death.

Ethical approval

Informed consent was obtained from the family for the purpose of writing this case report for publication.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: FM; data collection: SI; draft manuscript preparation: FM, SI, FCC. All authors reviewed the results and approved the final version of the manuscript.

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Case Report

Successful desensitization protocol for pyridostigmine in a 12 year old patient with myasthenia gravis

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ABSTRACT

Background. Myasthenia gravis is a chronic, autoimmune disease with muscle weakness. Acetylcholinesterase inhibitors are used in the symptomatic treatment of the disease. Allergic reaction to pyridostigmine bromide is rare. In the literature, no allergic reaction to pyridostigmine bromide has been reported in the pediatric population.

Case. A 12-year-old female patient diagnosed with myasthenia gravis consulted our clinic with the complaint of urticaria due to pyridostigmine bromide. The oral challenge test performed with pyridostigmine bromide was positive. As the patient was required to be continue pyridostigmine bromide with no suitable alternatives, it was decided that the patient had to be desensitized to pyridostigmine. During and after the desensitization protocol, no reaction was observed.

Conclusions. In this report, a successful desensitization protocol for pyridostigmine bromide in a child with myasthenia gravis is discussed.

Key words: allergy, desensitization, myasthenia gravis, pyridostigmine bromide.

Myasthenia gravis is a chronic autoimmune disease affecting the neuromuscular junction. In this disease, autoantibodies are formed against acetylcholine receptors located in the postsynaptic membrane of striated muscles. These autoantibodies may cause muscle weakness in patients. Muscle weakness can be generalized or localized. Generally, proximal muscles are affected more often than distal muscles. Since the disease often affects the eye muscles, diplopia and ptosis may occur. Muscle weakness may increase with exercise and fatigue. Complaints of patients tend to increase significantly towards the evening.[1]

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Annual incidence is 8 to 10 cases per 1 million individuals, and the prevalence is 150 to 250 cases per 1 million. Myasthenia gravis is the most common disease affecting the neuromuscular junction. Diagnosis of myasthenia gravis, the symptoms and signs of the patient are determined by electrophysiological tests, the Tensilon test and the demonstration of positive autoantibodies.[2]

The most commonly used drugs in the treatment of myasthenia gravis are acetylcholinesterase inhibitors. Acetylcholinesterase inhibitors act by slowing the degradation of acetylcholine at the neuromuscular junction, prolonging the interaction of acetylcholine with its receptor on the muscle membrane and enhancing neuromuscular transmission. Pyridostigmine bromide is the most commonly used acetylcholinesterase inhibitor.[1,3]

Pyridostigmine bromide has various side effects. Gastrointestinal side effects, such as abdominal cramping, loose stool and

flatulence, are the most common. Increased perspiration and muscle twitches and cramps are other side effects.[3] Allergic reaction to pyridostigmine bromide is rare.[4] To our knowledge, in the literature, no allergic reaction to pyridostigmine bromide has been reported in the pediatric population. Here, a successful desensitization protocol is described in the first reported pediatric myasthenia gravis case who developed an immediate type hypersensitivity reaction due to pyridostigmine bromide.

Case Report

A 12-year-old girl with myasthenia gravis presented to our clinic with the complaint of urticaria after using pyridostigmine bromide. In the patient's history, it was learned that the patient was diagnosed with myasthenia gravis and 60 mg pyridostigmine bromide was administered three times a day as a treatment. Twenty minutes after taking the drug on the seventh day of her treatment, urticaria developed on the dorsal side of her feet and arms (Fig. 1, 2). She had no other complaints. There was no history of any allergic disease in the patient's medical history. She had no allergic reaction to any drug or food in the history.

The patient was treated with an oral antihistamine. Then, the patient underwent an oral challenge test with pyridostigmine bromide after 4 weeks. We started the oral challenge test with 18 mg pyridostigmine bromide and

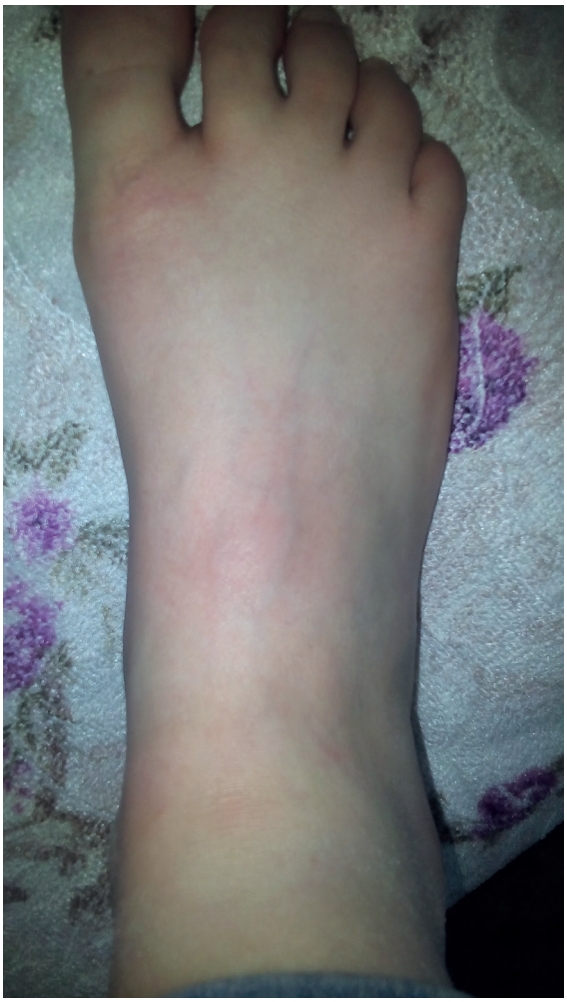

Fig. 1. Urticarial lesions on her foot.

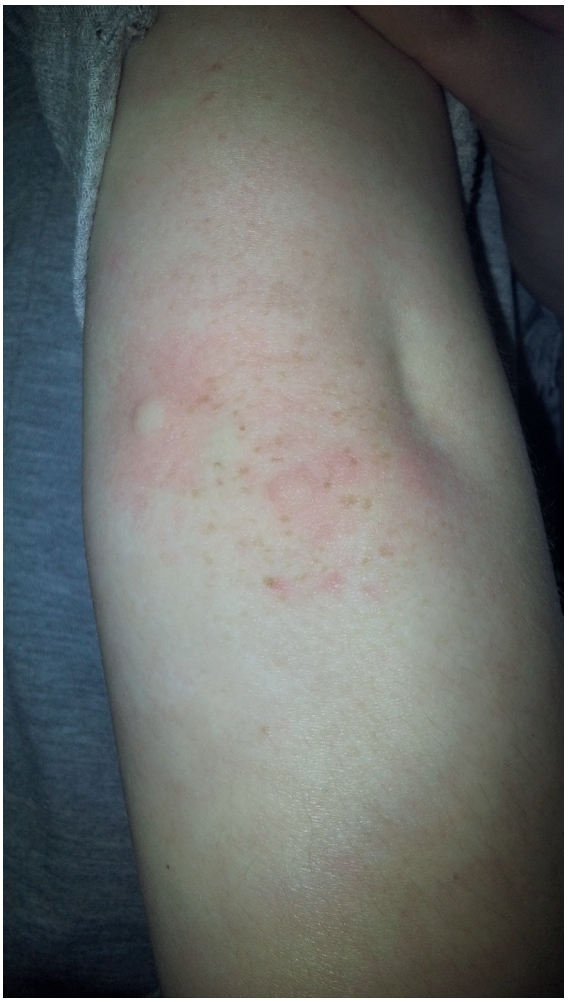

Fig. 2. Urticarial lesions in her arm.

Table I. Desensitization protocol for pyridostigmine bromide.

Time (minute)	Dose (mg)
0	0.6
30	1.8
60	5.4
90	16.2
120	36

doubled the dose every thirty minutes. In the third step of the oral challenge test the patient developed urticaria and flushing. Oral challenge test was accepted as positive.

The only drug used in the symptomatic treatment of myasthenia gravis in Türkiye is pyridostigmine bromide. Therefore, desensitization to pyridistigmine was decided for this patient. Written informed consent was taken from the patient's parents before the desensitization protocol. Premedication was performed with pheniramine, methylprednisolone and ranitidine before the initiation of the desensitization protocol. We started desensitization with 1/100 of the target dose and tripled the dose every thirty minutes. Desensitization for pyridostigmine bromide consisted of five steps and took 120 minutes in total (Table I). During and after the desensitization protocol, no reaction was observed. The patient continues the pyridostigmine bromide treatment at the normal dose.

Discussion

Myasthenia gravis is a chronic, autoimmune disease. It significantly impairs the quality of life of patients due to muscle weakness. Acetylcholinesterase inhibitors used in the treatment reduce muscle weakness by preventing the breakdown of acetylcholine, allowing it to stay in the synaptic gap longer.[3] Therefore, the they are indispensable for the treatment of myasthenia gravis. Pyridostigmine bromide is the only drug used in the symptomatic treatment of myasthenia gravis in Türkiye. Other acetylcholinesterase inhibitors neostigmine bromide and ambenonium chloride are not available. Therefore, we applied desensitized our patient to pyridostigmine bromide. To our knowledge, this is the first case of successful desensitization in a pediatric patient who developed immediate type hypersensitivity reaction to pyridostigmine bromide.

Acetylcholinesterase inhibitors may have various side effects. Gastrointestinal side effects, such as abdominal cramping, loose stool, and flatulence, are most common. Increased perspiration and muscle twitches and cramps are other side effects.[3] Immediate type hypersensitivity reaction to pyridostigmine bromide are rare.[4,5] However, Immediate type hypersensitivity reactions have not been reported in the pediatric population. To our knowledge, our patient is the first case who developed an immediate type hypersensitivity reaction to pyridostigmine bromide.

In patients with drug allergies, desensitization is administered only if it is absolutely required to administer the medication and no alternative treatment is available. The objective of desensitization in such patients is to temporarily suppress the response of the body to the medication. The patient is ensured to be administered with the medication without developing any reaction by administering the medication, starting with a low dose and increasing the dose gradually. Desensitization protocols are required to be based on general rules and be simple, safe, easy and amendable in accordance with the response of the patient. The initial dose for desensitization should be determined based on the severity of the reaction. Typically, the initial dose is required to be within the range of 1/100.000 and 1/100 of the complete therapeutic dose.[6] We initiated the dose of 1/100 of pyridostigmine bromide for our patient and reached a complete therapeutic dose, increasing by three-fold for each step. No reaction developed at any of the desensitization steps.

In conclusion, although rare, an immediate type hypersensitivity reaction can be occur with pyridostigmine bromide in patients diagnosed with myasthenia gravis. Desensitization is vital and inevitable for myasthenia gravis patients who develop urticaria to pyridostigmine bromide. The protocol that we propose here encompasses the general rules of desensitization: a regimen that is safe, simple, and effective. Although desensitization procedures have been conducted by different specialists, for the patient's safety, allergists should develop, review, and supervise treatments.

Ethical approval

Written informed consent to publish the case, was given by the patient's parents.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: FK, ET; data collection: FK; analysis and interpretation of results: FK, ET; draft manuscript preparation: FK, ET. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

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Case Report

Catastrophic antiphospholipid syndrome accompanied by complement regulatory gene mutation

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ABSTRACT

Background. Antiphospholipid syndrome (APS), particularly the catastrophic antiphospholipid syndrome (CAPS), is one of the rare causes of thrombotic microangiopathy (TMA). CAPS is the most severe form of APS, especially when accompanied by complement dysregulation, causes progressive microvascular thrombosis and failure in multiple organs. In this report, a case of CAPS with TMA accompanied by a genetic defect in the complement system is presented.

Case. A 13-year-old girl was admitted to the hospital with oliguric acute kidney injury, nephrotic range proteinuria, Coombs positive hemolysis, refractory thrombocytopenia, a low serum complement C3 level and anti-nuclear antibody (ANA) positivity. The kidney biopsy was consistent with TMA. She was first diagnosed with primary APS with clinical and pathological findings and double antibody positivity. As initial treatments, plasmapheresis (PE) was performed and eculizumab was also administered following pulse-steroid and intravenous immunoglobulin treatments. Her renal functions recovered and she was followed up with mycophenolate mofetil, hydroxychloroquine, low dose prednisolone and low molecular weight heparin treatments. The patient presented with severe chest pain, vomiting and acute deterioration of renal functions a few months after the diagnosis of TMA. A CAPS attack was considered due to radiological findings consistent with multiple organ thrombosis and intravenous cyclophosphamide (CYC) was given subsequent to PE. After pulse CYC and PE treatments, her renal functions recovered, she is still being followed for stage-3 chronic kidney disease. Complement factor H-related protein I gene deletion was detected in the genetic study.

Conclusions. The clinical course of complement mediated CAPS tends to be worse. Complement system dysregulation should be investigated in all CAPS patients, and eculizumab treatment should be kept in mind if detected.

Key words: antiphospholipid antibody syndrome, thrombotic microangiopathy, complement activation, human complement factor H-related protein.

Antiphospholipid syndrome (APS) is an autoinflammatory disease characterized by arterial/venous thrombosis and/or recurrent pregnancy losses. The disease may be seen as primary or secondary to other autoinflammatory diseases such as systemic lupus erythematosus (SLE). The presence of anticardiolipin antibody (ACA), anti-beta 2 glycoprotein 1 antibody (anti-β2GP1) and lupus anticoagulant (LAC) is required for diagnosis.[1,2] Catastrophic antiphospholipid syndrome (CAPS), a life-threatening subgroup of APS, is characterized by multiple thrombosis and organ failure that

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develops within days.[1,2] Because of its high mortality rate (33-50%), early recognition is important.[1] CAPS is typically characterized by microthrombosis, whereas medium and large vessels are involved in APS. Systemic inflammatory response syndrome (SIRS) may also develop due to excessive cytokine release in CAPS.[1]

Thrombotic microangiopathy (TMA) is characterized by microthrombotic hemolytic anemia, thrombocytopenia and involvement of various organs. Antiphospholipid syndrome, especially the catastrophic form, is a rare cause of TMA due to characteristic microvascular involvement. Endothelial and/or complement activation play a crucial role in the pathogenesis of CAPS.[3] Additionally, it is important to recognize the crosstalk between the coagulation and complement systems. Complement activation due to various complement regulatory gene mutations seen in CAPS patients causes more serious complications.[3] The most common complement gene mutation in these patients is the complement factor H-related protein (CFHR) deletions.[3] Herein, a case of CAPS with TMA accompanied by a genetic defect in the complement system is presented.

Case Report

A 13-year-old female was admitted to the hospital with abdominal pain and swelling on both knees. Her medical history revealed that thrombocytopenia was detected during her hospitalization for severe menstrual bleeding two months ago. On admission, she had diffuse edema and decreased urine output; blood pressure was 163/100 mmHg. Bicytopenia was detected in the complete blood count, and the hemoglobin and platelet counts were 9.7 gr/dl and 35.000/mm^3, respectively. Her laboratory and clinical findings indicated oliguric acute kidney injury (AKI), serum urea and creatinine levels were 209 mg/dl and 3.97 mg/dl, respectively. Nephrotic range proteinuria (46 mg/m^2/h) was detected in 24-hour collected urine, but the serum albumin level (3.6 g/dl) was normal. Hemodialysis was initiated because of volume load and acute hypertensive encephalopathy unresponsive to antihypertensive drugs and diuretics. Schistocytes were detected in her peripheral smear. Anti-nuclear antibody (ANA) and direct Coombs were positive. Laboratory findings showed reticulocytosis (4%), low serum haptoglobulin (<8 mg/dl) and elevated LDH (1080 U/L) levels consistent with hemolysis. There was no evidence of malignancy in the bone marrow aspiration. The patient was considered to have TMA. Serum complement C3 level was low (72 mg/dl, normal range: 88-201 mg/dl), ADAMTS-13 enzyme level and activity (130.94 IU/ml and 94%, respectively) were normal. A renal biopsy was performed because of prolonged oliguric course and to detect the etiology of AKI. Pathological examination showed glomerular congestion, polymorphonuclear leukocyte infiltration, fibrin thrombi in capillary loops and cortical necrosis consistent with the clinical diagnosis of TMA (Fig. 1). No specific finding of lupus nephritis was detected in the kidney biopsy. Three doses of pulse-steroid (methylprednisolone, 30 mg/kg/dose) and intravenous immunoglobulin (1 gr/kg single dose) treatments were given and high dose oral prednisolone (60 mg/m^2/day) and mycophenolate mofetil (800 mg/m^2/day) were continued as there was still clinical suspicion of SLE. Plasmapheresis (nine sessions, 1.5 fold of estimated plasma volume, replaced with fresh frozen plasma) was performed to clear out possible sources of antibody and complement-related TMA, and the patient received three doses of eculizumab (600 mg/dose). After twenty days on hemodialysis, her urine output increased and her blood pressure stabilized at normal percentiles.

The differential diagnosis of cortical necrosis and thrombosis was evaluated. The anticardiolipin antibody was negative. Lupus anticoagulant (Screen levels 123.3

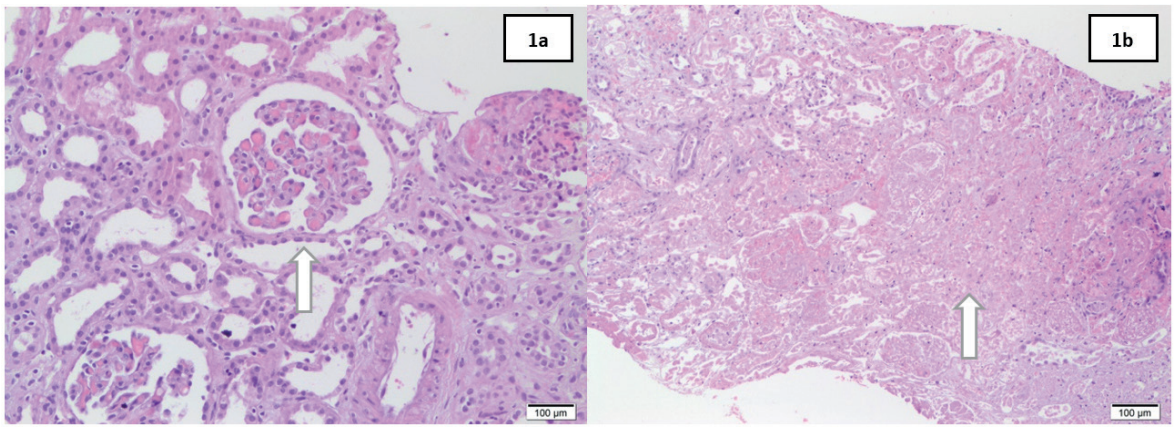

Fig. 1. Histopathological findings of kidney. (a) H&E staining shows fibrin thrombi in glomerular capillary loops (Hematoxylin-eosin stain, original magnification ×100) (b) H&E staining shows a wide cortical necrosis in the right side (Hematoxylin eosin stain, original magnification ×100)

and 93.5 seconds respectively, normal range: <44 seconds; confirmation levels 48.5 and 40.4 seconds respectively, normal range: <37 seconds; and screen/confirmation ratio: 2.54 and 2.31 respectively, normal range: <1.3) and anti- β2GP1 IgM (31.25 and 41.38 RU/ml respectively, normal range: 0-19 RU/ml) were found to be positive twice, 12 weeks apart. The patient was diagnosed with primary APS with histopathology and antibody positivity (Table I). She was followed up with mycophenolate mofetil (800 mg/m^2/day), hydroxychloroquine (5 mg/kg/day), low dose prednisolone (5 mg on alternate days) and low molecular weight heparin (2000 IU/day) treatments. Our patient's urine output increased first, then her eGFR increased to 41 ml/min/1.73m^2. Hemodialysis was discontinued after a significant recovery of kidney functions.

Table I. Antiphospholipid syndrome (APS) and catastrophic APS diagnostic criteria[1,7]

Antiphospholipid Syndrome Diagnostic Criteria*	
Clinical	Laboratory
1) Vascular thrombosis	1) Lupus anticoagulant
• One or more arterial, venous, or small vessel thrombosis in any tissue	- At least 2 times, 12 weeks apart
2) Prenatal mortality	2) Anticardiolipin antibody
• One or more unexplained fetal deaths >10 weeks	- IgG and/or IgM
• Preterm birth of one or more normal fetuses <34 weeks	- At least 2 times, 12 weeks apart
• Three or more <10 weeks unexplained miscarriage	Medium and high titer
	3) Anti beta-2 glycoprotein 1 antibody
	- IgG and/or IgM
	- At least 2 times, 12 weeks apart, high titer
Catastrophic APS Diagnostic Criteria**	
• Involvement of at least 3 organs, tissues or systems	
• Organ manifestations develop within a week	
• Antibody positivity (high titer)	
• Exclusion of other causes	

*2006 Sydney Criteria, 1 clinical and 1 laboratory criteria must be met.
**All criteria must be met.

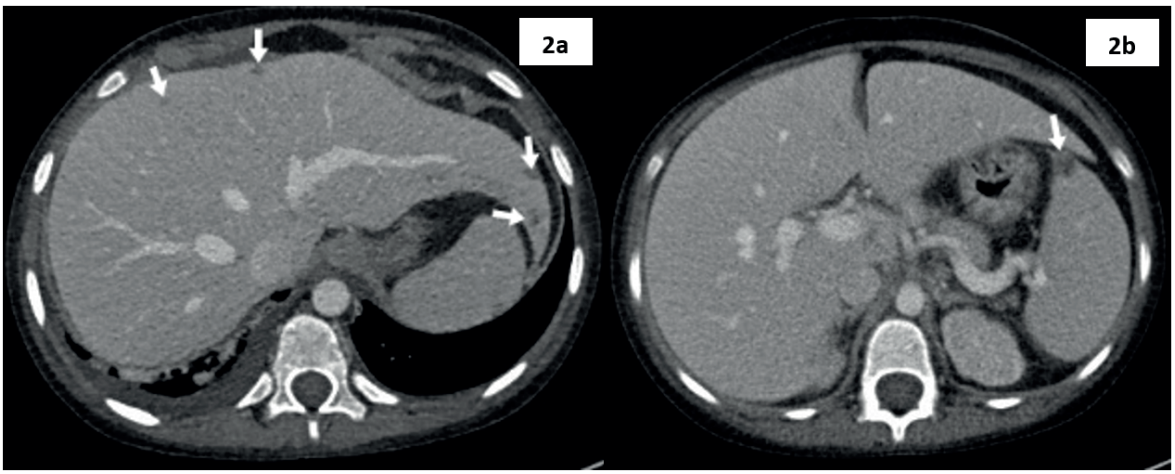

Fig. 2. Radiological findings. Ischemic areas are visible in intravenous contrast-enhanced abdominal computed tomography: (a) subcentimetric hypodense areas (arrow) in both lobes of the liver, and (b) a hypodense area (arrow) in the anterior midsection of the spleen.

She was readmitted to the hospital after two months due to severe chest pain and vomiting. Clinical and radiological investigations revealed acute deterioration of chronic renal damage, as well as hepatic and splenic ischemia (Fig. 2). CAPS was considered with clinical findings and multiple ischemic lesions (Table I). Intravenous cyclophosphamide (1000 mg/m^2/dose) was given subsequent to the three sessions of plasmapheresis (1.5 fold of estimated plasma volume, replaced with fresh frozen plasma). After three doses of pulse cyclophosphamide, she is still being followed for stage-3 chronic kidney disease (eGFR 45 ml/min/1.73m^2 with Schwartz formula), clinically stable with oral mycophenolate mofetil (800 mg/m^2/day), hydroxychloroquine (5 mg/kg/day), low-dose prednisolone (5 mg on alternate days) and low molecular weight heparin (2000 IU/day) treatments. Because of the widespread thrombosis with multiple organ involvement, genetic studies were done. Genetic analysis revealed a large deletion in the *CFHR1* gene (exon 2, 3, 4), however, the anti-factor-H antibody was negative.

Biochemical and mutational analysis

Anti-cardiolipin antibody and anti-β2GP1 were measured by enzyme-linked immunoassay (ELISA), according to the manufacturer's protocol. Values for ACA >12 IU/ml and anti-β2GP1 >19 RU/ml were identified as positive. The simplified Dilute Russell's Viper Venom Test (dRVVT) was performed for LAC1 screening reagent and LAC2 confirmatory reagent according to the manufacturer's protocol. Lupus anticoagulant was considered positive when the dRVVT ratio (LAC1 screen/LAC2 confirmation) was above 1,3.

For genetic studies, after detailed informed consent was obtained, the patient's total genomic DNA was extracted from peripheral blood using the QIAamp DNA Mini Kit (Qiagen, Hilden, Germany). *ADAMTS13*, *C3*, *CD46*, *CFH*, *CFB*, *CFHR1 (NM_002113.2)*, *CFI*, *DGKE*, *MMACHC* and *THBD* genes were sequenced using the Sophia Clinical Exome Solution (CES) kit via Next-Generation Sequencing (NGS) (Illumina Nextseq 500). Bioinformatic analyzes and variant sequencing were performed using the Sophia-DDM-V3 bioinformatics analysis program. Based on the ClinVar database, only pathogenic and possibly pathogenic variants associated with the patient's clinic were reported. Retained variants were evaluated according to the American College of Medical Genetics and Genomics (ACMG) 2015 guideline. Data from the 1000 Genome Project, database of

Single Nucleotide Polymorphisms (dbSNP) and Exome Aggregation Consortium (ExAC) were used as the control population.

An informed consent was received from the patient's family about the publication of this report.

Discussion

CAPS is a rare disease characterized by progressive microvascular thrombosis and failure in multiple organs or systems and diagnosed by the presence of responsible antibodies and exclusion of other etiologies. It may be primary or secondary to autoinflammatory diseases such as SLE or APS. Anti beta-2 glycoprotein 1, LAC and ACA are detected at high titers in patients' sera twice at least 12 weeks apart.[1,2] There is usually a trigger to initiate the inflammation and thrombosis cascade, especially infections and malignancies.[1,3] This entity is distinguished from severe APS by the type of affected vessel and the evidence of a systemic inflammatory response. While thrombosis in medium and large vessels is commonly seen in APS, microvascular involvement is typical for CAPS. In addition, SIRS is also a distinctive clinical finding for CAPS compared to APS.[1] CAPS is a rare clinical entity that occurs in approximately 1% of patients with APS.[4] According to the international CAPS registry, CAPS was the first presentation form of APS in 86% of pediatric patients.[5] In the same study, 60 of 500 (12%) patients had symptoms before the age of 18; these were predominantly female (67%) and primary CAPS (59%). The association with autoinflammatory diseases is less in CAPS compared to APS. According to the Pediatric-APS registry, 49% of patients with APS had an underlying autoimmune disease, compared to 24% of patients with CAPS.[1] The diagnosis is delayed mostly due to the similarity of clinical and laboratory findings with other autoinflammatory diseases and unfortunately its mortality rate is about 33-50% if untreated.[5,6] Although TMA is a rare condition in APS, it can be seen especially in patients with CAPS which is characterized by microvascular thrombosis. Our patient was considered to have primary APS because there were no clinical, laboratory, or pathological findings of any concomitant autoinflammatory disease.[1,7]

There are many theories concerning the pathophysiology of CAPS, the best known are; excessive cytokine release, thrombosis, endothelial injury and complement activation.[1-3] Usually, a bacterial or viral product and lipopolysaccharides initiate inflammation and bind to Toll-like receptor 4, allowing the release of proinflammatory cytokines. This inflammatory environment itself provides a prothrombotic basis.[8,9] Besides, anti-β2GP1 antibodies directly induce endothelial cell activation and promote platelet aggregation and adhesion.[1,10] Thrombosis is a crucial finding in several complement-related diseases, such as paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome (aHUS).[11,12] Although the mechanism of complement activation is unclear in CAPS, it is obvious that a crosstalk between evolutionarily related complement and coagulation pathways has a critical role in thrombosis formation, as a "third hit" in the pathogenesis that aggravates the basal procoagulant and inflammatory state, and in turn worsens the clinical course.[1,3,13-16] Activated C3a and C5a, alternative pathway members of the complement system, provides the release of pro-inflammatory and pro-coagulant cytokines from monocytes and endothelial cells. The terminal pathway product C5b-9 also induces the release of procoagulant vWF and P-selectin.[3] Several animal studies have shown that C3a-receptor knock-out mice are less susceptible to experimental thrombosis.[17] A prospective experimental study evaluating complement activation in APS/CAPS patients with modified Ham assays by complement-dependent cell death and cell surface depositon of C5b-9 by flow cytometry, resulted in significantly higher complement activation in CAPS (85.7%) against APS (35.6%) and SLE (6.8%) patients. Likewise, patients with CAPS are more likely to have

mutations in complement dysregulatory genes (60%) compared with patients with APS (21.8%) or SLE (28.6%) or normal controls (23.3%) and have a similar incidence to patients with aHUS (51.5%).[3] In conclusion, besides endothelial cell activation, anti-β2GP1 antibody activates complement system and contributes to the formation of thrombosis, also accompanied complement dysregulation causes more severe thrombotic tissue damage especially in CAPS patients, like in our patient. In addition, the detection of renal cortical necrosis associated with extensive thrombosis in the pathological examination of our patient was also assumed to be an effect of the *CFHR1* mutation. In our case, the low C3 level at admission was one of the indirect indicators of complement activation. Normal C4 levels also supported the diagnosis of primary CAPS by reducing the possibility of diseases such as SLE that activate the complement system via the classical pathway. The lack of SLE-specific findings in kidney biopsy also supports this hypothesis.

In recent years, limited studies have revealed that there are some complement gene variants associated with CAPS. Patients with CAPS were found predominantly to have homozygous *CFHR1-CFHR3* deletions.[3] This is a relatively common genetic variation that occurs in 2% of the general population.[18] However, their product CFHR proteins have a prominent role in complement regulation by competing for factor H or inhibiting C5 convertase activity directly.[19] Commonly, *CFHR1-CFHR3* deletions are seen together with the presence of an anti-factor H antibody that inhibits factor H functions.[20,21] Anti-factor H is one of the common complementopathies in aHUS etiopathogenesis but to the best of our knowledge, no anti-factor H antibody-associated CAPS cases has been reported. Similar to previous studies, our patient has a large *CFHR1* deletion and the anti-factor H antibody was negative.

Eculizumab, a long-acting C5 blocking antibody, has been used for many years especially for aHUS and some other complement-related diseases.[13,22-24] Eculizumab inhibits the formation of pro-inflammatory and pro-thrombotic C5a and C5b, thus preventing the formation of the membrane attack complex.[12] In recent years, there have been many case reports showing the success of eculizumab therapy in CAPS patients; who were resistant to anticoagulant, immunosuppression and plasma exchange therapies.[3,13,25-27] According to the pathogenesis of thrombosis in CAPS, blockage of the complement system can prevent wide-spread thrombosis and/or poor clinical outcome. We believe that the presented patient with acute renal damage who required dialysis responded effectively to eculizumab treatment in the first attack, and eculizumab can be administered again if CAPS attacks recur due to the genetic mutation we found in the patient. Eculizumab treatment should be kept in mind in CAPS patients, especially in genetic forms and as a prophylaxis after transplantation, according to the clinical course and response to classical treatments.

Antiphospholipid syndrome should be considered in patients presenting with TMA especially with an atypical medical history such as refractory thrombocytopenia. CAPS, a subgroup of APS, is a rare and mortal entity which is characterized by multiple organ failure within days. However, mortality decreases with early diagnosis and effective treatment especially in complement mediated CAPS. Complement system dysregulation should be studied in all patients. Mutations associated with complement system dysregulation tend to be seen with a severe clinical course in patients with CAPS. Complement system blockage with eculizumab is promising for treating patients with CAPS.

Ethical approval

An informed consent was received from the patient's family about this report.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: IG; data collection: SP, IG; interpretation of results: EDB, SG, NÇ, MS, ÖNT, DF, CP, BS, HA; draft manuscript preparation: SP, IG; critically review of the manuscript: EDB, SG, NÇ, MS, ÖNT, DF, CP, BS, HA. All authors reviewed the manuscript and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Case Report

Successful treatment of post-pericardiotomy syndrome via C1 inhibitor replacement therapy in a hereditary angioedema patient with Marfan syndrome

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ABSTRACT

Background. Hereditary angioedema with C1 inhibitor deficiency (HAE-C1INH) is caused by dysfunctional C1-INH protein due to mutations in the *SERPING1* gene encoding C1-INH. Marfan syndrome is a genetic connective tissue disease that affects the cardiovascular and ocular systems along with the skeletal system. In this case, we present the successful treatment of post-pericardiotomy syndrome unresponsive to classical therapy, which has not been described in the literature. The syndrome developed in a patient with hereditary angioedema (HAE) who underwent open heart surgery due to cardiac involvement in Marfan syndrome.

Case. A nine-year-old male HAE-C1INH patient underwent open heart surgery secondary to cardiac involvement caused by Marfan syndrome. To prevent HAE attacks, 1000 units of C1 inhibitor concentrate therapy were given 2 hours before and 24 hours after the operation. Post-pericardiotomy syndrome was diagnosed on the postoperative second day and ibuprofen 15 mg/kg/day (3 weeks) was started. Since there was no response to classical treatment on the 21st postoperative day, C1 inhibitor concentrate treatment was planned as 1000 units/dose for 2 days a week considering a prolonged hereditary angioedema attack. In the second week of treatment, complete recovery was achieved for pericardial effusion with a total of 4 doses.

Conclusions. We emphasize that in patients with hereditary angioedema undergoing this treatment, care should be taken in terms of complications that may be associated with the disease even if short-term prophylaxis is given before operations and that longer-term use of C1 inhibitor concentrate has a place in treatment.

Key words: hereditary angioedema, Marfan syndrome, post-pericardiotomy syndrome, C1 inhibitor replacement therapy.

Hereditary angioedema (HAE) is a rare potentially life-threatening autosomal dominant disease characterized by episodes of cutaneous and submucosal edema. It is estimated to occur at a rate of 1/50,000 that varies in different regions.[1-3] The main abnormality is a deficiency/defect of C1 inhibitor (C1-INH) protein or other mechanisms. Genetically identifiable forms of hereditary angioedema (HAE) are listed in Table I. The genetic defects in Type 1 and Type 2 are mutations in the *SERPING1* gene, which encodes the functional C1-INH protein that regulates multiple proteases involved in the complement contact system, coagulation, and fibrinolytic pathways.[2] However, de novo mutation of *SERPING1* is responsible for the disease in approximately 20-25% of patients. Type I HAE is present in 85% of patients and type II HAE affects the remaining 15%.[4,5]

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Table I. Genetically identifiable forms of HAE

Type of HAE	Underlying defect
HAE-1 (Type 1 HAE)	C1-INH deficiency (low antigenic and functional C1-INH levels
HAE-2 (Type 2 HAE)	C1-INH dysfunction (normal or elevated antigenic but low functional C1-INH levels)
HAE-FXII	Mutation in the factor XII gene
HAE-ANGPT1	Mutation in the angiopoietin-1 gene
HAE-PLG	Mutation in the plasminogen gene
HAE-KNG1	Mutation in the kininogen 1 gene
HAE-MYOF	Mutation in the myoferlin gene
HAE-HS3ST6	Mutation in the heparan sulfate 3-O-sulfotransferase 6 gene
HAE-UNK	Patients without known mutations have been described.

C1-INH: C1-inhibitor, HAE: hereditary angioedema

Cutaneous edema attacks are the most common symptoms and occur in >95% of patients. Patients often experience recurrent abdominal pain caused by bowel wall angioedema. Laryngeal edema is the most serious complication seen in 50% of patients and can be life-threatening if not treated promptly. Symptoms are usually self-limiting and progress within hours, with the frequency of attacks ranging from once a week to several attacks per year.[6-8] Although its clinical manifestations usually begin in the first and second decades of life, delay in accurate diagnosis and the inadequacy of effective therapeutic approaches have hindered effective management of the disease until recently. With the introduction of C1 inhibitor concentrations, successful results were obtained from both short-term and long-term prophylaxis of HAE attacks and acute attack treatment.[2]

Marfan syndrome (MFS) is a genetic connective tissue disease that affects the cardiovascular and ocular systems along with the skeletal system. It is characterized by a qualitative/quantitative disorder of fibrillin synthesis as a result of a defect in the fibrillin gene (*FBN1*) on chromosome 15.[9] In this case, we present a previously unreported association of Marfan syndrome and hereditary angioedema, as well as the successful treatment of post-pericardiotomy syndrome unresponsive to classical ibuprofen therapy.

Case Report

A 9-year-old male patient was admitted to an external center due to recurrent penile/testicular swelling that started at the age of 4 years. Since his father had a diagnosis of HAE type 2, examinations about C1-INH were as follows: C1-INH level: 72.3 mg/dl (n:21-39), C1-INH activity: 27.4% (n:70-130), C4: <6.65 mg/dl (n:10-40). On genetic examination, a heterozygous p.Arg466Cys (c.1396C>T) mutation was detected in *SERPING1*, and he was diagnosed with HAE Type 2. In addition, aortic root dilatation, mitral valve prolapse, and mitral insufficiency were detected in the postnatal 6th month, and genetic examination revealed heterozygous p.Gly1226Val (c.3677G>T) mutation in the 29th exon of the *FBN1* gene, and a diagnosis of Marfan syndrome was made. The patient, who was planned to have open heart surgery with the Bentall procedure (because of the risk of perforation of the aortic valve that may be caused by excessive enlargement of the aortic diameter), was admitted to our hospital's pediatric allergy clinic 4 months prior for management of the process and the follow-up of the disease. According to the HAE on-demand treatment protocol, 1000 units of C1-INH concentrate treatment was applied for 2 hours before the operation and in the 24th hour after the operation. In addition, 3 units of fresh frozen plasma (FFP) were administered during the operation which lasted for a total of 6 hours,

165 minutes of which was on cardiopulmonary bypass. During intubation and extubation, no complication was seen. On the second day after the operation, echocardiography revealed posterior pericardial fluid and post-pericardiotomy syndrome was considered. Ibuprofen 15 mg/kg/day (3 weeks) and colchicine 1 mg/kg/day were started. As pericardial fluid did not decrease on the 21st postoperative day, prolonged hereditary angioedema attack could not be excluded. C1-INH concentrate treatment was planned as 1000 units/dose for 2 days/week. Pericardial fluid regression was observed on the control echocardiography at the end of the first week and the treatment was continued. Complete recovery was achieved for pericardial effusion with a total of 4 doses. Informed consent was obtained from the family for the publication of the case report.

Discussion

Marfan syndrome, a systemic disorder of connective tissue, is a disease with a wide phenotypic spectrum associated with heterozygous *FBN1* pathogenic variants. In MFS, there are mainly ocular, skeletal and cardiovascular system involvements. Major morbidity and early mortality in MFS are related to the cardiovascular system; dilatation of the aorta at the level of the sinuses of valsalva, mitral and tricuspid valve prolapse, and enlargement of the proximal pulmonary artery may be seen. Stretching of the aortic valve annulus due to aortic root enlargement can cause leaflet faulty coaptation and aortic valve regurgitation. In pediatric patients with MFS, moderate to severe aortic valve regurgitation was found to be a predictor of aortic root enlargement and cardiovascular events such as death and aortic dissection. Aortic valve insufficiency has become an important feature in prophylactic surgery indications with the introduction of valve-sparing aortic root replacement techniques.[10,11]

The classical complement, coagulation cascade and antifibrinolytic systems are inhibited by the C1 esterase inhibitor. Failure to prevent complement activation leads to increased production of C2 kinin and bradykinin. The released substances induce endothelial cell retraction in the post-capillary venules, causing cavities and plasma leakage, leading to angioedema. Hereditary angioedema associated with a hereditary deficiency of C1 esterase inhibitor is characterized by recurrent episodes of painful swelling in the subcutaneous and/or submucosal tissues.[8]

There are three different types of management in the treatment of C1-INH-deficient HAE: on-demand therapy (during acute attacks), management of attacks with short-term or procedural prophylaxis, and long-term prophylaxis. Most drugs used in the treatment of HAE are not approved for use in children, and data about safety and efficacy are lacking. Therefore, plasma-derived C1-INH was recommended as first-line therapy for short- and long-term prophylaxis, as well as for the treatment of acute attacks in children.[2]

HAE attacks are often unpredictable, but a dental or medical procedure such as surgery, trauma, or stress is known to be a trigger for an attack. A preventive management plan before such situations can reduce the risk of HAE attacks. The probability of angioedema attack increases up to 30% after a surgical procedure without prophylaxis.[12] In addition, surgery and cardiopulmonary bypass (CPB) are known to activate the complement cascade and increase the risk of angioedema.[13] Tanaka et al.[14] reported data on 13 patients with type 1/2 HEA who underwent cardiac surgery, 7 of them received preoperative C1-INH supplementation. No cardiac complications were observed in any of these patients. Only one patient had swelling in the lower back and lips on the 2nd postoperative day, treated with 1000 IU of C1-INH as a precaution, and these symptoms resolved

within 2 hours.[15] Preoperative replacement with C1-INH (1000 IU or 20 IU/kg) 1-6 hours before major surgery is recommended. It is known that plasma C1-INH activity increases by 2.2% for every 1 IU/kg. Theoretically, although the actual efficacy among HAE patients is highly variable, the reported C1-INH activity after one dose of C1-INH (1000–1500 IU) appears to be consistent with its pharmacokinetics.[13,14] Cardiovascular surgery and CPB may affect intraoperative C1-INH activity after preoperative replacement. The C1-INH level is affected not only by the plasma half-life of each product, but also by the kallikrein-kinin system, complement activations and contact coagulation after initiation of CPB. Ongoing bleeding, fluid replacement, and blood administration (other than plasma) can progressively reduce C1-INH activity. C1-INH activity decreases by 30-50% from baseline after CPB. Postoperative supplementation of C1-INH may be considered if low-grade bradykinin formation persists and a delay in classical pathway activation occurs 24-48 hours after surgery.[16]

In the literature, there was a patient with aortic aneurysm who developed ascites, hypovolemic shock, and acute renal failure following a HAE abdominal crisis triggered by spontaneous retroperitoneal bleeding. Although this patient received renal dialysis, assisted ventilation, blood transfusions, daily danazol (200 mg) and intermittent C1-INH concentrate, good clinical response could not be obtained. For this reason, daily C1-INH concentrate was applied for 21 days (1000 units per day). After 4 days of C1-INH treatment, renal functions, abdominal ascites, and pneumonia also clinically improved gradually.[17]

Prolonged HAE attack terminology has not yet been used in the literature. HAE symptoms are generally worse during the first 24 hours and gradually subside in severity over the following 2 to 5 days. We used prolonged HAE attack terminology in our case report since there was no response to classical treatment for post-pericardiotomy syndrome on the 21st postoperative day. However C1 inhibitor concentrate treatment of 1000 units/dose for 2 days a week resulted in complete recovery of pericardial effusion with a total of 4 doses. We assume overactivation of complement cascade and factor XII due to the usage of heparin-protamine complexes during cardiac surgery.[13] In addition, ongoing bleeding and fluid replacement may progressively reduce C1-INH activity. C1-INH activity decreases by 30-50% from baseline after CPB.[16] On the other after tissue injury, damage-associated molecules, such as S100 and the high mobility group box 1 (HBGM1) proteins, defensins, lectins, cardiolipin, cellular DNA and dsRNA, and even intact mitochondria, occur in the extracellular microenvironment. Interaction of these molecules with multiligand receptors, activate the cellular and molecular effector mechanisms of the innate immune system, including activation of the clotting and complement system, acute phase protein and pentraxin production, and the cellular inflammatory responses. It means that there is more complement activation in patients with C1 inhibitor deficiency, as in our patient. However, in experimental, studies C1 inhibitor concentrate improves healing and re-epithelialization.[18] Inadequate wound healing especially in cardiac surgery may lead to the presence of cell residues that cause continuous complement activation in HAE patients and may prolong the HAE attack.

In our case, although he received both preoperative prophylaxis and postoperative C1-INH treatment, post-pericardiotomy syndrome developed, and there was no response to ibuprofen and colchicine treatment. Since prolonged hereditary angioedema attack could not be excluded, C1-INH concentrate treatment was given and pericardial effusion was completely resolved with 4 doses. Our patient is the first case in the literature who developed post-pericardiotomy syndrome despite having received both preoperative prophylaxis and postoperative C1-INH. On the other hand, a different treatment modality was attempted and achieved successful results.

At the same time, this is the first case with two orphan diseases, HEA and Marfan syndrome, in the literature.

In conclusion, in patients with hereditary angioedema, care should be taken in terms of complications that may be associated with the disease even if short-term prophylaxis was given before an operation, and the necessity of longer-term administration of C1 inhibitor concentrates in treatment should be kept in mind.

Ethical approval

Informed consent was obtained from the family for the publication of the case report.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: NMG, ET; data collection: HDS; analysis and interpretation of results: ED, FG, HDS; draft manuscript preparation: NMG, ET. All authors reviewed the results and approved the final version of the manuscript.

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Case Report

Endoscopic treatment of periampullary duodenal duplication cyts in an 18-month-old girl

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ABSTRACT

Background. Duodenal duplication cysts (DDC) are rare congenital anomalies of the gastrointestinal tract and periampullary localization with anatomical variants including biliary and pancreatic duct anomalies remains a surgical challenge. Endoscopic treatment of the periampullary DDC (PDDC) communicating with the pancreaticobiliary duct in an 18-month-old girl is presented to discuss the endoscopic treatment options in children.

Case. An 18-month-old girl with a normal prenatal ultrasound (US) was asymptomatic until complaining of abdominal pain and vomiting at 10-months of age. Abdominal US revealed a 1.8 × 2 cm cystic mass adjacent to the second part of the duodenum. The amylase and lipase levels were slightly increased while she was symptomatic. Magnetic resonance cholangiopancreaticography (MRCP) showed a thick cyst wall measuring 1.5 × 2 cm at the second part of the duodenum, consistent with DDC that was suspected to be communicating with the common bile duct. Upper gastrointestinal endoscopy confirmed a bulging cyst in the duodenum lumen. The puncture and injection of the cyst with contrast material confirmed the communication of the duplication cyst with the common bile duct. The unroofing of the cyst was performed with endoscopic cautery. The biopsy obtained from the cystic mucosa revealed normal intestinal histology. Oral feeding was initiated six hours after the endoscopy. The patient has been followed for the last 8 months uneventfully.

Conclusions. Endoscopic treatment of PDDC with various anatomical variants can be considered an alternative to surgical excision in children.

Key words: periampullary, duodenal duplication cyst, endoscopy, children.

Duodenal duplication cysts (DDC) are rare congenital anomalies of the gastrointestinal (GI) tract and constitute 5-7% of all GI duplication cysts.[1] Two embryologic theories have been proposed to explain the development of DDC. They may occur due to duodenal epithelial pinching during the outgrowth of the dorsal pancreatic bud or secondary to epithelial sequestration.[1] DDC are typically adherent to the mesenteric site of the third or fourth part of the duodenum and are made up of an epithelial mucosal lining and a smooth muscle layer.[2]

DDCs localized adjacent to the major papilla and biliary-pancreatic papilla with or without an aberrant pancreatic duct draining into a cyst are defined as periampullary DDC (PDDC).[1] Periampullary type is much rarer and shows a more variable clinical presentation including pancreatitis, bleeding, duodenal obstruction and perforation.[3]

Although endoscopic treatment of PDDC is well defined in the adult population, there is little information regarding the use of endoscopic treatment in children. Bulotta et al.[3] reported

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4 pediatric cases managed with endoscopic intervention and reported favourable outcomes in children aged 11 to 14 years. However, the availability of endoscopic treatment in PDDC for small infants has not been reported. Therefore, an 18-months-old girl with PDDC is reported to discuss the technical tricks and results of endoscopic management of PDDC in young children.

Case Report

A girl weighing 3100 grams was born to a 29-year-old mother at the 38th week of gestation. The prenatal ultrasound (US) was normal and the patient was asymptomatic until 10 months of age. After complaining about abdominal pain and vomiting an abdominal US was performed, revealing a 1.5 x 2 cm cystic mass adjacent to the duodenum (Fig. 1). At the time of the symptoms, the complete blood count and liver function tests were normal. There was a slight increase in lipase (115 U/L normal: < 67 U/L) and pancreatic amylase (125 U/L, normal: 8-53 U/L) levels. The total (0.38 mg/dL, normal: 0.3-1.2 mg/dL) and direct bilirubin levels (0.083 mg/dL, normal: 0-0.2 mg/dL) were also within normal limits. Magnetic resonance cholangiopancreaticography (MRCP) revealed a thick-walled cyst adjacent to the second portion of the duodenum and pancreas, which was consistent with DDC and suspected to communicate with the common bile duct (Fig. 2). After obtaining consent from the parents, the patient underwent an endoscopic evaluation under general anaesthesia. The body weight of the patient was 12 kg at the time of the endoscopic evaluation. The procedure was performed using an adult therapeutic duodenoscope (PENTAX, ED-3490TK, Japan). The cyst was bulging at the second portion of the duodenum (Fig. 3a). The papilla was on the proximal side of the cystic protrusion. The cyst was punctured with a sclerotherapy needle (Micro-Tech Endoscopy, China) and contrast material was injected into the cyst (Fig. 3b). After confirming the communication of cysts with the common bile duct, incision of the cyst wall with a needle knife sphincterotome (Boston Scientific, USA) was performed with an electrosurgical generator (Olympus, ESG-100, pulse cut slow, (Fig. 3c). A biopsy was obtained from both the cyst wall and the inner layer of the cystic cavity. The histopathological evaluation of the biopsies revealed duodenal epithelium in the cyst wall confirming the diagnosis of DDC (Fig. 4). There were no perioperative and postoperative complications, and the patient was fed orally 6 hours after the operation. The patient was released from the hospital the next day and has been monitored for the past eight months without incident. Long-term follow-up is planned for possible malignant transformation.

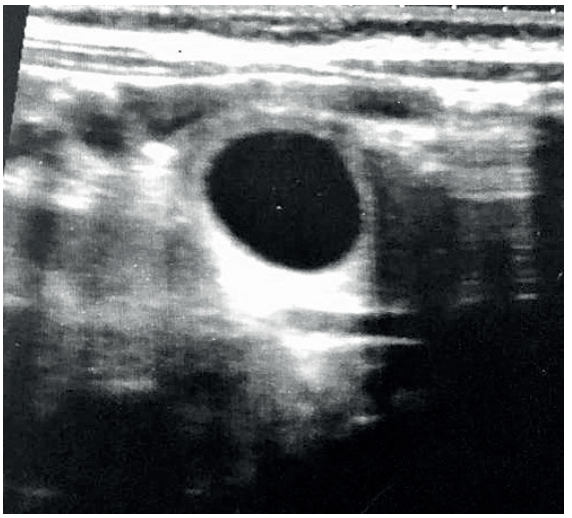

Fig. 1. Ultrasound image shows thick-walled duodenal duplication cyst.

Discussion

PDDC are extremely rare type of duplication cysts in the GI tract and constitutes a major surgical challenge because of the close localization to the biliary and pancreatic tree. Endoscopic treatment of PDDC enables better definition of the intra-luminal cyst, accurate localization of the papilla and distinguishes PDDC from other cystic lesions.[3] Although endoscopic treatment of PDDC is well defined in adults, there is scant information for the pediatric population. In a literature search, Bulotta et al.[3] reviewed 20 pediatric cases with

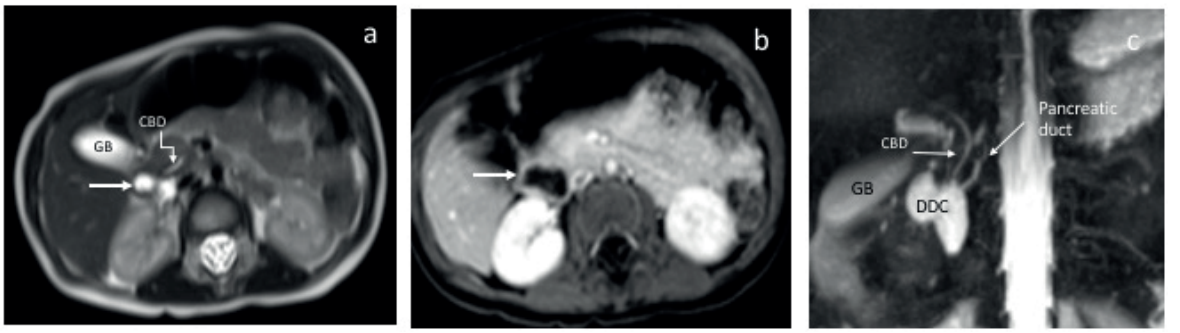

Fig. 2. (a) Axial T2-weighted, and (b) postcontrast T1-weighted, (c) coronal T2-weighted MRCP images show the duodenal duplication cyst (arrows in a and b) adjacent to the duodenum and the pancreas. CBD: common bile duct, DDC: duodenal duplication cyst, GB: gallbladder, MRCP: magnetic resonance cholangiopancreatography.

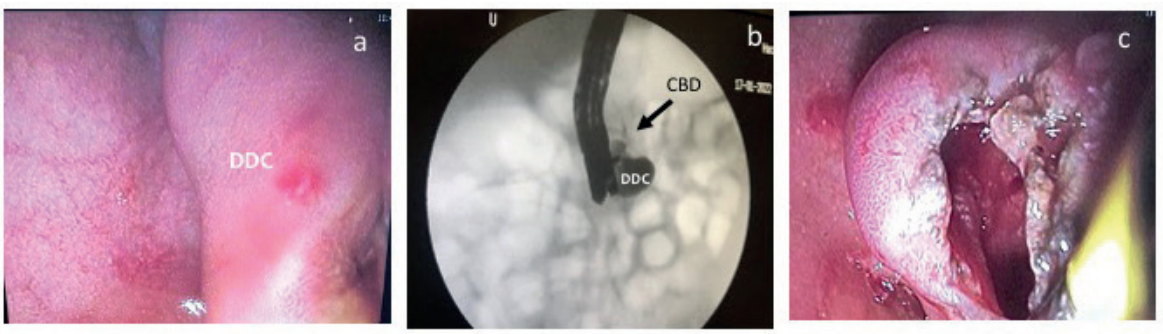

Fig. 3. Endoscopic diagnosis and treatment of periampullary DDC: (a) DDC bulging into the lumen of second part of the duodenum. (b) The contrast material injected to the cyst confirms the communication of the cyst with the common bile duct. (c) Unroofing of the cystic wall with endoscopic cautery. CBD: common bile duct, DDC: duodenal duplication cyst.

PDDC and only 50% of them were managed endoscopically. The median age of the patients was 14 years and the youngest patient was 3 years-old.[3,4] Herein, we report the youngest case of successful endoscopic management of PDDC in children.

Abdominal pain, vomiting and clinical findings of pancreatitis are common presentations of PDDC in children. In addition to the localization and size of the cysts, the patient may have a variety of symptoms due to anatomical variations. Pancreatitis may occur due to external obstruction of the papilla or obstruction due to debris or mucus secreted from the cyst. The biliary sludge in the pancreatic duct may also be seen in DDC. Therefore, detailed evaluation of anatomical variation is mandatory to differentiate DDC from other cystic lesions especially from common bile duct cysts.

US is highly suggestive for DDC. An outer hypoechoic muscle layer with an internal echoic inner layer suggests a duplication cyst. Although US is used as the first diagnostic tool, more comprehensive radiologic evaluation is needed to define the anatomical variations.[5] Preferably, MRCP can be used to define the communication between the pancreatic duct and the cyst.[6] Therefore, we performed MRCP and suspected that both the common bile duct and pancreatic duct were draining into the cyst.

Moreover, endoscopic evaluation is also useful to define the major papilla and obtain an endoscopic retrograde cholangiopancreatography (ERCP). In patients with large cysts, filling the lumen of the duodenum, the major papilla cannot be defined and it may not possible to obtain an ERCP. Therefore, we suggest that endoscopic injection of contrast material is a good option

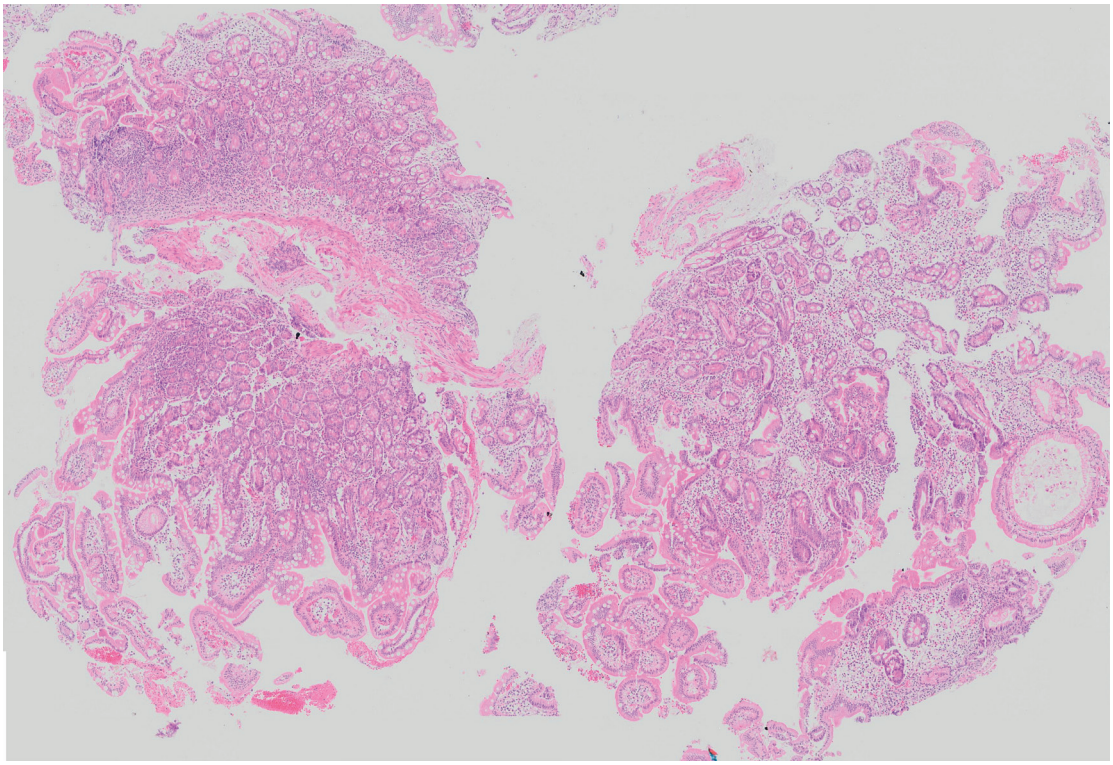

Fig. 4. The biopsy obtained from the cyst wall revealed duodenal epithelium (H&E stain).

to confirm the communication of the DDC with the biliary and pancreatic duct.

The surgical resection of PDDC can be demanding and may cause severe complications in small children. Endoscopic treatment consists of incision of the cyst wall, marsupialization, unroofing and sphincterotomy if needed.[4] Needle-knife, sphincterotome and endoscopic cautery can be used for cyst incision.[4] Although removing the cystic mucosa is recommended to prevent malignant transformation, endoscopic treatment of PDDC is highly effective for relieving symptoms. Endoscopy has several advantages over surgical excision. It enables direct visualization of the cystic mass in the duodenum and provides accurate localization of the papilla.[3] Endoscopic excision is well tolerated even in small children, with better cosmetic results and fewer complications. Although endoscopic incision of PPDC in small infants is not technically demanding, puncture of the bulging cyst may be needed in small children to have a wider working space. Finally, it has no visible scars and can be performed on an outpatient basis. The most important disadvantage of endoscopic treatment is that it leaves gastric and pancreatic mucosa with the potential for malignant complications.[7] Therefore, all parents should be informed about the risk of malignant transformation and close follow-up with endoscopic surveillance and/or radiologic imaging should be recommended.

Bleeding is an important but very rare complication of the endoscopic incision of the PDDC. It can be treated with metallic clips and blood transfusion.[3] This complication can be easily prevented by using endoscopic cautery, and in most of the cases early oral feeding can be initiated.

The differential diagnosis of PDDC from other cystic lesions, particularly choledochocele, is critical. Although some authors consider biopsy of the cyst wall to be the gold standard, intestinal mucosa has also been reported in

choledochocele.[8] However, a biopsy of the cyst wall should be routinely performed for histologic confirmation. Moreover, Antaki et al. reported that the normal-looking papilla was always found on the proximal side of the protrusion, whereas it is usually found on the distal side of the protrusion in choledochoceles.[9] In our patient, the papilla was on the proximal side of the cystic protrusion, which suggests a PDDC more than a choledochocele.

Although, DDCs are benign lesions, a few cases of malignant transformation have been reported.[7,10] Several years after endoscopic treatment, it has been reported that asymptomatic adult patients have undergone malignant transformation. Therefore, long-term follow-up is recommended, particularly in patients treated endoscopically.[3] Despite the fact that there is no clear recommendation about follow-up periods in endoscopically treated patients, asymptomatic cases can be evaluated by US, whereas endoscopic evaluation is needed in symptomatic cases.

In conclusion, endoscopic treatment of PDDC with various anatomical variants can be considered an alternative to surgical excision in children. It is an easy and safe procedure, even for young patients. Long-term follow-up is mandatory for endoscopically treated patients because of the potential risk of malignancy.

Ethical approval

Informed consent was obtained from the parents.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: TS, EP, data collection: ÖB, HBA; analysis and interpretation of results: BO, DO; draft manuscript preparation: TS, EP. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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NOTICE TO AUTHORS

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  - Funding
  - Conflict of interest
  - Acknowledgement
  - Authors contribution

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