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Aims and Scope

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

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

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

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Peer Review, Publication Ethics and Malpractice Statement

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Official Journal of Ege University Children's Hospital

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The
Journal of Pediatric Research
Official Journal of Ege University Children's Hospital

Contents

Original Articles

Case Report

The
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Editorial

Dear JPR Readers,

You are reading the first issue of the JPR of 2023. In this issue of the journal, we include 12 original articles and 1 case report. While we were preparing for this issue, we experienced a great tragedy in our country and the effects of this continue heavily on us. We are in mourning.

In Turkey, two earthquakes struck with magnitudes of 7.8 Mw and 7.5 Mw, taking place on February 6th, 2023, just 9 hours apart, with epicenters in the Gaziantep's Şehitkamil district and the Kahramanmaraş's Ekinözü district, respectively. As a result of these earthquakes, tens of thousands of people have lost their lives in Turkey and Syria, and hundreds of thousands have been injured. These two earthquakes in Turkey affected about 15 million people in an area of one thousand square kilometers. The Turkish Government has announced the highest level of emergency in this affected region, including calls for help from international organizations and foreign governments with expertise in emergencies such as natural disasters and epidemics. The World Health Organization has also declared a level 3 emergency for the earthquakes that shook Turkey. These earthquakes were the most destructive earthquakes causing the highest death toll among all the earthquakes which have occurred in Turkey. Health workers and volunteers from Turkey and many other countries have mobilized to assist in this great disaster.

In this issue of the journal, we include 12 original articles and 1 case report. Original studies covering current issues in many areas of pediatrics have been included. These are in the fields of neonatalogy, oncology, neurology, rheumatology, gastroenterology and pulmonology. You can also read original studies on the COVID-19 infection, which continues to affect the whole world. Again, in this issue, we have included a very rare case with neonatal lupus erythematosus, which we think will contribute to the literature.

With science, our loss of life and suffering will decrease, and our world will become more beautiful.

Best wishes

Samim Özen

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Original Article

Lung Ultrasound - Can it be Potentially Painful for a Newborn?

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ABSTRACT

Aim: We aimed to analyze changes in vital parameters and assess behavioral responses to lung ultrasound (LUS) in preterm and term newborns hospitalized in a neonatal intensive care unit (NICU).

Materials and Methods: Three groups of neonates (term, $37^{0/7}$-$41^{6/7}$ weeks; moderate to late preterm, $32^{0/7}$-$36^{6/7}$; and very preterm, $<32^{0/7}$) were included. Response to LUS was assessed using heart rate (HR), blood oxygen saturation (SpO_2), and the neonatal infant pain scale (NIPS). Reactions to LUS, blood sampling, and nappy change were compared.

Results: Seventy-one infants were enrolled: 30 term, 21 moderate to late preterm, and 20 very preterm. An increase in mean HR and a decrease in median SpO_2 during LUS were observed ($p<0.001$) in all analyzed groups, whereas the median NIPS score was 3. During LUS, 38% of term infants experienced pain according to NIPS. The same was observed for 47% and 35% of infants in the moderate to late preterm and very preterm groups. The trend of NIPS increased along with the higher intensity of the stimulus. The highest NIPS values were related to blood sampling, moderate to LUS, and the lowest to nappy change ($p<0.001$).

Conclusion: As LUS affects vital parameters and may be perceived as potentially painful in >1/3 newborns, indications for each examination and adequate pain management should always be considered.

Keywords: Newborn, pain, lung ultrasound, response, neonatal infant pain scale

Introduction

In recent years, the importance of lung ultrasound (LUS) in neonatal intensive care units (NICUs) has increased significantly. It has been successfully used for the diagnosis, management, and monitoring of most pleural and pulmonary pathologies in newborns, such as pneumonia, pneumothorax, pleural effusion, and respiratory distress syndrome (1-5). In comparison with chest radiography, the main advantage of LUS is the absence of ionizing radiation, which guarantees the safety of serial imaging in extremely vulnerable neonates (6,7). Moreover, LUS is non-invasive, relatively low-cost, and can be performed at the point-of-care, which is especially important when managing critically ill, unstable patients in the NICU environment (8). Although ultrasound has been shown to cause harmful thermal and mechanical bio-effects in animal models (9-11), recent studies have not confirmed these findings in clinical settings (12). Therefore, neonates admitted to NICU are often subjected to numerous ultrasounds, especially in their first days of life.

Despite the many advantages of LUS, it remains unclear whether it can be undoubtedly classified as a neutral

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stimulus in infants. It is intuitively regarded as a non-painful procedure since it is not related to tissue damage. However, LUS may cause discomfort to infants, as it requires the use of gel, the pressure of the ultrasound probe, and regularly changing of the newborn's position. To date, an analysis of short-term behavioral reactions and changes in vital parameters in newborns undergoing LUS has not been performed. Moreover, whether premature infants respond differently to LUS compared with term newborns has not been evaluated.

The assessment of pain intensity in neonates remains challenging and is currently based on analyzing changes in their behavior and vital parameters, such as their heart rate (HR), respiratory rate, blood pressure, and blood oxygen saturation (SpO_2). Over 40 neonatal pain assessment tools, which include different combinations of these indicators, are available (13). One of the most popular is the Neonatal Infant Pain Scale (NIPS), which is dedicated to procedural pain assessment in both preterm and term neonates. The NIPS has been successfully tested for validity and reliability in the neonatal population (14,15).

The main aim of this study was to analyze changes in vital parameters and evaluate behavioral response in order to identify potential pain related to LUS in premature and term neonates hospitalized in the NICU. The other objective was to compare infants' reactions to LUS and other painful and neutral procedures.

Materials and Methods

Study Design

This study was conducted in a tertiary referral NICU. The research design is illustrated in Figure 1. Reactions to three different stimuli were analyzed for each patient: LUS and two control procedures. Blood sampling was chosen as the painful control procedure, while nappy change was used as the neutral control stimulus. The responses to each procedure were analyzed on different days in the morning between 6 and 9 a.m., before any other nursing or diagnostic actions, with at least a 1 hour interval after feeding. The procedure order was randomly established. The hospital stay was prospectively analyzed for the number of painful stimuli experienced by the newborns. The application of the methods of procedural pain management was also investigated.

Sample

Infants hospitalized in the NICU were enrolled into this study. The patients were divided into three groups based on their gestational age (GA): term ($37^{0/7}$-$41^{6/7}$ weeks), moderate to late preterm ($32^{0/7}$-$36^{6/7}$ weeks), and very preterm (<$32^{0/7}$ weeks). Patients were considered for this study if they were in a stable medical condition defined as the absence of invasive ventilation or cardiovascular support. The exclusion criteria included the occurrence of major malformations, severe intraventricular hemorrhage (IVH grade IV), and earlier hospitalization in neonatology units longer than 3 days. The analysis of the infants' responses was performed after the completion of 35 weeks of postmenstrual age (PMA) in preterm newborns and before discharge in term neonates.

Procedures

All ultrasounds were performed by one certified sonographer who was experienced in LUS using Phillips HD 11 (Philips, Amsterdam, the Netherlands) or Hitachi-Aloka Arietta v70 (Hitachi, Tokyo, Japan) scanners with a linear probe of 12-5 MHz. Five lung areas were routinely examined: anterior (midline), anterior (right), anterior (left), posterior (right), and posterior (left), using the transversal and longitudinal positions of the probe. If the infant was supine, the anterior parts of the lung were assessed first. Subsequently, the posterior fields were examined after changing to the prone position. If the patient was in the prone position, the LUS was started with posterior field scans. For all examinations, the ultrasound gel was warmed. The probe was disinfected before and after each LUS. The blood samples were obtained from each patient through a peripheral vein puncture or heel lance. The blood sampling was performed by qualified nurses. Each patient underwent a nappy change procedure, which included toileting of the recto-genital region using wet nappies. For standardization, the nappy change was carried out by the same researcher every time. In order not to increase exposure to procedural pain or stress, the analysis of the infants' response to each procedure was performed only on the occasion of routine daily care or when it was regarded as diagnostically necessary by the attending physicians.

Instruments

All infants were continuously monitored using pulse oximeters as part of their routine medical care in the NICU. Before beginning this study, the baseline HR and SpO_2 of the participants were noted. Subsequently, during the entire procedure, the infants' vital parameters were evaluated for maximal HR (HR max) and minimal SpO_2 (SpO_2 min) values. After completing the procedures, the recovery times were analyzed, which was defined as the time that elapsed

until HR and SpO_2 returned to their baseline values. It was measured separately for each parameter to an accuracy of 1 second using a stopwatch. The maximum observation time was 300 seconds. Additionally, ΔHR was calculated as the difference between the HR max and the baseline HR. Finally, ΔSpO_2 was estimated by subtracting SpO_2 min from the baseline SpO_2.

Continuous video recordings of the infants during each procedure were performed using a digital camera (SONY HDR-CX250E). Subsequently, all recordings were archived in order to assess pain intensity with the use of NIPS. The total pain score ranges from to 0-7. Values of >3 indicate pain (15). The videos were analyzed by two independent observers who were experienced in NIPS evaluation. The final NIPS result was calculated as the average of the results obtained from the two observers.

Statistical Analysis

Statistical analysis was performed using Statistica software, version 13.3 (TIBCO Software Inc. Palo Alto, CA, USA). The results are presented based on the parameters of descriptive statistics, including mean values and standard deviations (SD), or median values with first and third quartiles (Q1, Q3) for continuous variables and numbers with percentages for categorical variables. To confirm the normal distribution of continuous variables, the Shapiro-Wilk test was used. The assessed groups were compared using the Kruskal-Wallis test, and the ***t***-test was used for dependent samples. The Wilcoxon test was performed to analyze changes in vital parameters during LUS. Friedman's rank test was performed to compare the infants' responses during different procedures. The Jonckheere test was applied to evaluate the trend of NIPS changes with the increase in the intensity of the stimuli. The Spearman rank test was used to assess the correlation between HR, SpO_2, and NIPS values. The NIPS values were analyzed for inter-observer agreement using Kendall's coefficient of concordance. Statistical significance was set at p-values of <0.05.

Ethical Standards

Written formal consent was obtained from all of the legal guardians of the newborns. This study was approved by the Ethics Committee of Jagiellonian University (approval number: 1072.6120.112.2018).

Results

Study Population

Seventy-one infants hospitalized in the NICU between June, 2018 and March, 2021 were enrolled. The study cohort consisted of 30 term neonates (Group 1), 21 moderate to late preterm (Group 2), and 20 very preterm infants (Group 3). The detailed characteristics of the assessed groups are presented in Table I.

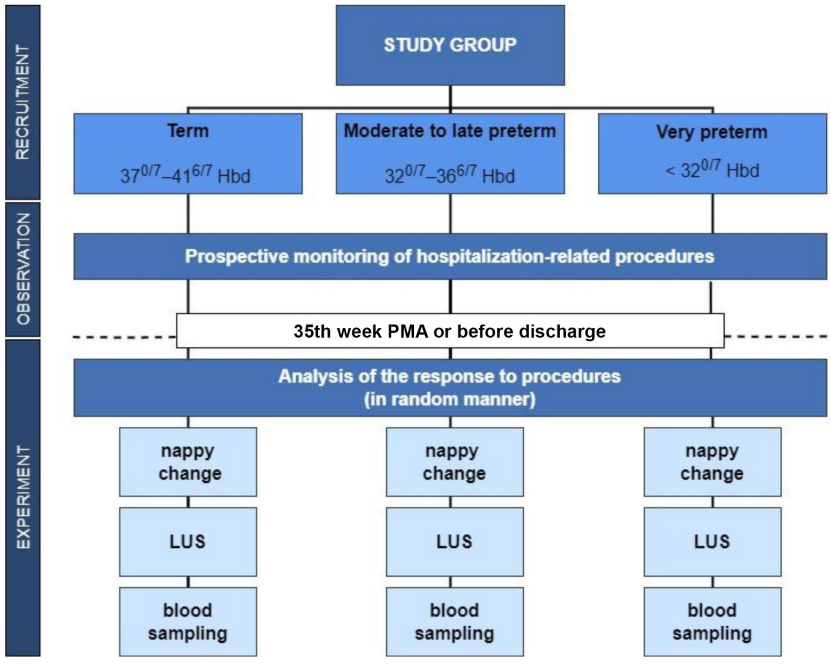

Figure 1. Study design
PMA: Postmenstrual age, LUS: Lung ultrasound

Procedural pain management

During the analyzed procedures, the patients received methods of non-pharmacological analgesia including non-nutritive sucking, oral glucose, maternal milk feeding, or a combination of those methods. Pharmacological treatment was not used for pain relief, but three patients received it for other reasons coincidentally.

Changes in vital parameters during LUS

In all analyzed groups, the mean HR increased significantly during LUS (Figure 2). A decrease in SpO_2 values was also observed in both term and preterm infants (Figure 3). The median change in the vital parameters during LUS in all the groups did not differ (p=0.08 for ΔHR and p=0.91 for ΔSpO_2). The median time of HR recovery was 27 seconds for term neonates, 72 seconds for moderate to late preterm neonates, and 66 seconds for late preterm neonates (p=0.11). Very preterm infants were characterized by the highest median time of SpO_2 recovery (14 seconds), whereas term and moderate to late preterm neonates obtained similar median values (8 seconds and 7 seconds, respectively; p=0.52).

Evaluation of pain intensity during LUS and control procedures

The values of Kendall's coefficient of concordance revealed a high level of agreement in NIPS evaluation between the two raters (Table II). During LUS, the median NIPS score was 3 in all analyzed groups. A total of 38% of term infants experienced pain according to NIPS (>3), whereas these rates were 47% of neonates from the moderate to late preterm group and 35% of neonates from the very preterm group. The analysis of perinatal history and hospitalization-related parameters did not reveal any predisposing factor to overreaction to LUS. In term and moderate to late preterm infants, NIPS scores were positively correlated with HR

Table I. Characteristics of the assessed groups

Group characteristics	Term	Moderate to late preterm	Very preterm
Male	17 (56.67%)	12 (57.14%)	9 (45%)
Gestational age (weeks)	39 (38-40)	33 (33-35)	28 (27-30)
Birth weight (g)	3,340±520	2,080±570	1,220±360
Cesarean section	13 (43.33%)	18 (85.71%)	17 (85%)
1st minute Apgar score (pt.),	7 (4-10)	7 (6-9)	6 (4-6)
Twin pregnancy	0 (0%)	6 (28.57%)	4 (20%)
Age at the admission (days)	1 (1-3)	1 (1-2)	1 (1-1)
Time from admission to analysis (days)	7±4	16±8	57±22

Data are presented as n (%), median (Q1-Q3), or mean ± SD
SD: Standard deviation

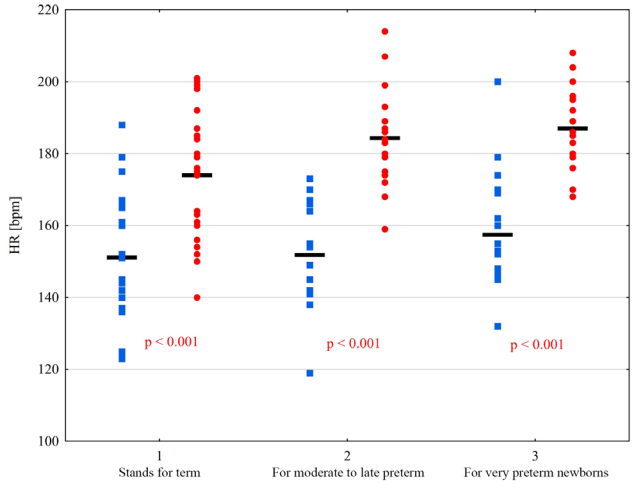

Figure 2. Change in HR during LUS
Black: Mean, Blue: HR before LUS, Red: HR max during LUS, HR: Heart rate

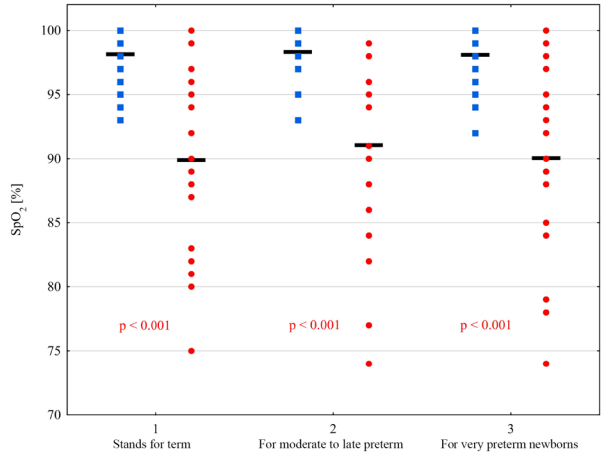

Figure 3. Change in SpO_2 during LUS
Black: Median, Blue: SpO_2 before LUS, Red: SpO_2 min during LUS, SpO_2: Blood oxygen saturation, LUS: Lung ultrasound

Table II. Inter-observer agreement in the NIPS assessment for different procedures		
Statistics procedure	**Kendall's coefficient of concordance**	**p-value**
Nappy change	0.94	**<0.001**
LUS	0.93	**<0.001**
Blood sampling	0.87	**0.001**
LUS: Lung ultrasound, NIPS: Neonatal infant pain scale		

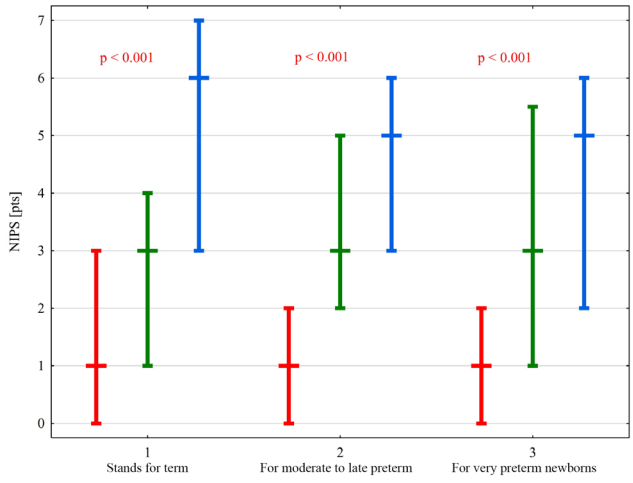

Figure 4. NIPS values during nappy change, LUS, and blood sampling. Data are presented as medians with quartiles
Red: Nappy change, Green: LUS, Blue: Blood sampling, NIPS: Neonatal infant pain scale, LUS: Lung ultrasound

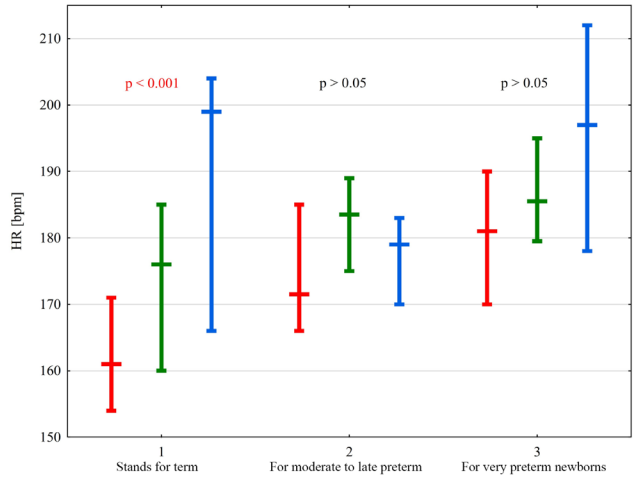

Figure 5. HR max during nappy change, LUS, and blood sampling. Data are presented as medians with quartiles
Red: Nappy change, Green: LUS, Blue: Blood sampling, HR max: Maximal heart rate, LUS: Lung ultrasound, HR: Heart rate

max (Rs=0.74, p<0.05, and Rs=0.47, p<0.05, respectively), while in very preterm neonates, a negative correlation with SpO_2 min was observed (Rs=-0.57, p<0.05). In all analyzed groups, the median NIPS values during LUS were higher than during nappy change and lower than during blood sampling (Figure 4). A significant trend of NIPS increase along with the higher intensity of the stimuli was observed in both preterm and term infants (p<0.001 for each group).

Change of vital parameters - comparison between procedures

In term neonates, the median value of HR max during LUS was significantly lower than during blood sampling (p<0.02) and did not differ from the median value during nappy change (p>0.05), whereas, in preterm infants, no difference in HR max was observed during the procedures (p>0.05) (Figure 5). SpO_2 min, HR, and SpO_2 recovery times were similar regardless of the type of procedure in all the analyzed groups.

Discussion

Despite major progress in neonatology, infants who are admitted to the NICU are still exposed to multiple painful procedures and require a long hospital stay. The systematic review by Cruz et al. (16) including six different studies revealed that hospitalized neonates experienced between 8 and 17 invasive procedures per day during their first two weeks of hospitalization. A study conducted by Lee et al. (17) showed that the median lengths of hospital stay in infants with low birth weight, very low birth weight, and extremely low birth weight were 21, 46, and 79 days, respectively. Thus, significant pain loads in newborns are an unquestionable problem. In particular, exposure to multiple painful procedures may have long-lasting effects on the postnatal process of central nervous system development. Repetitive pain cannot only prolong functional dysmaturity of the brain, but also induce permanent neuroanatomical changes, including reduced white matter and subcortical gray matter maturation, thalamic volume loss and decreased functional brain connectivity (18-21). The persistence of pathological reactions towards pain has also been observed (22,23). Thus, all procedures in the NICU environment should be carefully monitored for their indispensability and influence on neonates. Moreover, for all painful procedures, recommended evidence-based pain management should be implemented.

LUS has revolutionized the diagnosis of newborns. Its common use significantly decreases exposure to ionizing radiation and enables repetitive point-of-care lung imaging. Although the safety of ultrasound has been proven, the lack of side effects related to LUS should not be equated with painlessness. To the best of our knowledge, this is the first study to investigate changes in the vital parameters during LUS and to evaluate pain intensity using a scale dedicated to neonates.

Our study demonstrates that LUS is related to short-lasting disruption of crucial vital parameters, which can be observed in both term and premature infants of different GA. It seems that very preterm neonates require more time for SpO_2 and HR stabilization after stimulus, as they were characterized by the longest recovery times of the above parameters.

Although term and preterm infants obtained the same median NIPS values, which did not exceed 3 points, which was taken as the cut-off value for pain, in 35-47% of the evaluated neonates, the obtained scores were higher. The presence of procedural overreaction was previously reported by Chimello et al. (24) and was identified in approximately 1/3 of preterm infants. Further comparison of infants who experienced LUS as painful in comparison to those infants who did not experience the procedure as painful did not reveal any significant differences in their perinatal history or their course of hospital stay between the groups. The comparison between NIPS during LUS, nappy change, and blood sampling suggests that LUS should be classified as a procedure which moderately reduces the comfort of infants.

Premature babies were analyzed when they were stable and were already above 35 weeks PMA. We did not evaluate the reactions of babies in their first days of life; hence, we could not ascertain whether stimuli in this period may be even more dangerous. Our data cannot answer the above question, but they highlight its importance. The same question can be raised in unstable full-term newborns.

It may be argued whether the observed reactions are truly caused by pain, or they are rather manifestations of the stress experienced by newborns. Indeed, both stress and pain can manifest similarly in neonates. Behaviors associated with pain (such as grimace, changed breathing pattern, crying, and flexion of extremities) may accompany both painful and stressful procedures (25). Changes in vital parameters are also observed in both types of stimuli (25,26). The analysis of the pain concept by Fitri et al. (27) indicated tissue damage as the main attribute distinguishing neonatal pain from stress. As LUS is not related to the activation of nociceptors through tissue damage, it can therefore be intuitively classified as a stressful procedure rather than a painful one. However, The International Association for the Study of Pain emphasized that "pain and nociception are different phenomena" because pain is also strongly related to the psychological and subjective context (28). Moreover, not only can the clinical presentation of stress and pain be similar, but also their effects on the central nervous system can be similar. Studies based on functional magnetic resonance imaging showed that response to stress or pain may overlap in the amygdala, hippocampus, striatum, insula, and anterior cingulate cortex (29,30). Overall, as distinguishing between acute pain and stress in newborns is demanding in clinical and experimental settings and their effects may be similar, we postulate that strong stress and pain should be regarded as similar phenomena in newborns.

One of the main strengths of this study is the methodology of NIPS assessment, as it was based on video recordings and the evaluations were performed by two independent observers. A high inter-observer agreement guarantees good accuracy of these results and reduces observer bias.

Study Limitations

It should be emphasized that the group of term newborns assessed for this study was represented by a population with significant morbidity, which resulted in NICU admission. Hence, the main limitation of our study is that the obtained results cannot be generalized to healthy term neonates or those with only mild health issues.

Another limitation is related to the different time points of analysis of response to procedures in preterm and term newborns. Although all infants were examined in a similar PMA, the premature groups were characterized by an older chronological age. Hence, further studies are needed to compare reactions in the first days of life close to the expected date of delivery in preterm newborns.

Conclusion

Based on the obtained results, it should be emphasized that although LUS is a safe procedure, it should not be performed without limits and clinical indications, as it significantly affects critical vital parameters in neonates. Moreover, our study suggests that LUS can be classified as a procedure which is not neutral to infants. Some newborns may even perceive LUS as a potentially painful procedure, and the current level of knowledge does not allow them to be identified in advance, but in such cases, appropriate pain management should be always used.

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Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of Jagiellonian University (approval number: 1072.6120.112.2018).

Informed Consent: Written formal consent was obtained from all of the legal guardians of the newborns.

Authorship Contributions

Concept: M.O., P.K., Design: M.O., P.K., Data Collection and/or Processing: S.P.T., Analysis and/or Interpretation: P.K., Writing: M.O., S.P.T., P.K.

Conflict of Interest: None of authors have any conflicts of interest to report.

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Original Article

Are Oral Health Conditions Associated with Schoolchildren's Performance and School Attendance?

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ABSTRACT

Aim: To examine the relationship between children's oral health-related quality of life and their academic achievement and school attendance.

Materials and Methods: Data was gathered from the answers to a structured questionnaire from 150 children aged 7-12 years. Their demographic data, the children's/parents' oral health conditions, their academic performance/school absenteeism, and their intraoral examination outcomes were recorded via a structured questionnaire. The Silness & Löe plaque index was used to assess their dental plaque scores and DMFT/DMFS, dmft/dmfs indices according to the WHO criteria were used to determine their dental caries scores.

Results: The mean age of the 150 pediatric patients [72 girls (48%) and 78 boys (52%)] was 9.23±1.44 years. Due to dental care-related issues, 82% of schoolchildren missed less than two weeks, and 18% missed more than two weeks of school. Furthermore, 21% of these missed days were related to toothache or infections, and 34% were due to going to dental treatment appointments. The association between nail biting and hard object biting and the school achievement of the children was shown to be statistically significant (p=0.02 and p=0.03, respectively). According to the results of the present study, it was determined that school absenteeism was higher in those children who needed dental treatment. It was also observed that there was a negative correlation between school absenteeism and academic success (p=0.01).

Conclusion: Dental problems can cause school-aged children to be absent from school and affect their school performance negatively.

Keywords: Oral health-related quality of life, school absenteeism, school performance

Introduction

Oral health is one of the fundamental components of general health, and oral diseases impact the quality of life. The mouth is a conduit via which infectious organisms can enter the body, and dental health is regarded as a reflection of general health (1). Caries, dental pain, or periodontitis in children are considered oral health indicators (2). One of the most prevalent diseases in the world, dental caries, affects 60-90% of school-aged children. Especially, dental caries in primary dentition is a common public health challenge observed in approximately 621 million children (3). Feeding, breathing, speaking, smiling, and other physical and social functions, notably social adaptability, depend on good dental health (4).

Untreated dental caries result in pain, difficulty in feeding, weight loss, speech difficulties, and aesthetic problems. Children can miss school because of toothache, and in order to attend their dental appointment for caries

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treatment. Children who have oral diseases may experience discomfort, humiliation, delayed cognitive growth, low self-esteem, and/or difficulties in day-to-day activities (4).

Education is a critical component of both self-improvement and societal progression. It is essential to offer every child and teenager the chance to realize their full academic potential. Actually, many variables determine how students learn and perform in class. Some examples of factors which can affect academic performance are medical conditions, intellectual disability, psychological issues, school absenteeism and insufficient sociocultural context (5). It is accepted that poor dental health and unfavorable socio-economic circumstances negatively affect quality of life. In summary, oral health problems are medical conditions which can affect a child's education.

Attendance to school and academic performance are related to each other and indicators which affect a child's educational process (2,6). The issue of absenteeism from school is particularly significant since it may compromise children's quality of life by causing them to miss out on educational opportunities.

There are studies examining the relationship between dental health and academic performance in various regions. The relationships between children's oral health, academic achievement, and psychological status have been reported in the literature (7). However, there have been relatively few studies undertaken in Turkey.

The present study aimed to evaluate the association between oral health conditions and academic performance and school absenteeism in Turkish schoolchildren. This study hypothesized that children with poor oral health were more likely to have reduced school attendance and inadequate academic performance.

Materials and Methods

Ethical Considerations and Sample Selection

The present study was approved by the Ethical Committee of the Faculty of Medicine, Ege University (dated 20.04.2017 protocol number: 17-4/18). All children and their parents received written and verbal information about the procedure, and written informed consent was obtained before this study.

Study Design and Data Collection Tool

In the second part of the questionnaire, questions were asked about the children's academic performance and their school absenteeism. This part includes questions about their year-end achievement score, their homework status, and their total number of school days missed during the academic year because of toothache and/or dental treatment appointments. Furthermore, a question was asked to the parents in order to find out their point of view on whether there was any association between oral health conditions and a child's academic performance.

In the third part of the questionnaire, several questions were asked to determine the child's oral health conditions. These questions covered oral health topics such as the frequency of a child's tooth brushing, their consumption of sugary foods, and the presence of oral habits which cause malocclusion problems. In addition, past dental treatment experiences of the mother/father are investigated in the questionnaire.

In the last part of the survey, intraoral examinations were performed by a pediatric dentist. These intraoral examinations of the children were performed with the help of a mirror and a probe under a reflector light. The dental caries scores were recorded with DMFT/DMFS, dmft/dmfs indices according to the WHO criteria (8). The Silness & Löe plaque index was used to evaluate plaque scores in the children (9).

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA) with the chi-squared test, the Mann-Whitney U test, the Kruskal-Wallis test and descriptive statistics.

Results

Demographic Data

Seventy-eight male and 72 female participants (n=150) with a mean age of 9.23±1.44 years were included in this study. 32% of mothers and 44% of fathers' educational level was higher than 12 years. 78% of the parents lived together. 27% of the families had low income.

Academic Performance and School Absenteeism of Children

The year-end achievement scores of 19% of participants had points between 85-100 (very good), 62% of them had 70-84 points (good), 8% of them had 55-69 points (moderate), and 11% of them had 45-54 points (a passing grade). While 6% of students never did their homework, 36% did it sporadically, 49% usually and 9% did their homework consistently.

Seventy-six out of 150 parents reported school absenteeism in their children due to dental care-related

Table I. Association between caries groups and dental treatment-related absenteeism from school

		Caries free DMFT + dmft=0 (n)	Low caries DMFT + dmft=1-4 (n)	High caries DMFT + dmft>4 (n)	p-value
School Absenteeism due to dental care-related reasons	<2 weeks	8	19	35	0.02
	≥2 weeks	-	3	11	

reasons. 82% of schoolchildren missed less than 2 weeks and 18% of them missed more than 2 weeks due to dental care-related reasons.

21% of these missed days were explained by the presence of toothache or infection and 34% of these resulted from going for dental treatment. 77% of the parents believed there was a relation between the child's dental health and their academic performance but 23% of them did not agree with this idea.

A negative correlation was found between school performance and school absenteeism (p=0.01).

Children's and Parent's Oral Health Conditions

The children were asked how often they brushed their teeth, and 21% reported two to three times per day, 36% reported once per day, and 43% reported brushing their teeth irregularly.

24% of the children consumed sugary food only with their main meal, 41% of them 1-2 times, and 35% of them 2-3 times at times other than with their main meal. 65% of the mothers and 68% of the fathers had dental problems and treatment experiences in the past.

Bad oral habits which may cause malocclusion problems: nail biting (27%), prolonged use of bottles/pacifiers (23%), infantile swallowing (12%), thumb sucking (32%), tongue/lip/cheek biting (27%), mouth breathing (21%) and bruxism (44%) were observed in the patients. A statistically significant correlation was found between nail biting and hard object biting and their school performance (p=0.02 and p=0.03, respectively).

Intraoral Examination Outcomes

The caries index scores were grouped as follows; caries free: DMFT+dmft=0, low caries: DMFT+dmft=1-4, high caries: DMFT+dmft >4. A statistically significant correlation was found between the student's absenteeism from school due to dental treatment and their caries scores (p=0.02). Table I shows the relationship between the caries groups and absenteeism from school due to dental problems (dental caries, eruption problems, orthodontic anomalies).

When assessing the periodontal health of the children, the Silness & Löe plaque index was used to analyze their plaque scores, and their mean plaque value was reported to be 2.18. A statistically significant correlation was found between the student's absenteeism from school and their dental plaque scores (p=0.03).

Discussion

A child's dental health may have an effect on several aspects of their growth and development, as well as their overall health and quality of life (10). Despite recent advancements in the general quality of children's oral health, dental issues are still highly prevalent in young children. Oral health problems affect children's daily activities, according to studies which used quality of life as a metric for success. It has been noted in several studies that children with toothache have difficulty in concentration and learning and have low school success as a result of absenteeism from school due to dental pain or treatment. A significant association between dental caries and academic achievement has been reported in some articles in the literature (6,7,11-15), but not in others (2,16,17).

Gift et al. (18) conducted one of the first studies examining the relationship between dental health and academic performance. They discovered that 117,000 school hours were lost for every 100,000 American children. Another study showed that approximately 504,000 (7%) of California's 7,240,000 schoolkids ages 5-17 had missed at least one day of school due to a dental problem during a one-year period (19).

Six hundred primary schoolchildren's data were examined in India and their oral health status was recorded using the dft index according to the WHO criteria. The outcomes of that study established that the relationship between school performance and mean dft score was statistically significant, which is the same as the present study. Also, that study's results revealed a decline in the children's school performance due to the effects of poor dental health (11).

El-Sayed et al. (7) examined data from 380 Sudanese students and found that dental caries was highly related to poor academic performance, with statistically significant p-values of 0.008 and 0.023 for dmft and DMFT, respectively. In their study conducted with Sudanese children, only 1.73% of the 380 children were absent from school for more than 7-9 days due to dental treatment/pain; when compared to our study, this is a lower percentage (7). One hundred and fifty children participated in the present study, and 76 were absent from school due to dental problems/treatment. The absence of 18% of these children exceeded two weeks during the one-year period. When the results of another study involving one thousand and sixty-three 12- and 811 15-year-old Thai students were evaluated, it was discovered that one out of every 20 children was missing from school due to toothache (16). On the other hand, another study carried out in Thailand using data from 925 kids found no significant association between dental conditions and school achievement (20).

Almeida et al. (17) analyzed 374 children's data from Brazil and found that poor oral health status was not associated with school absence due to dental pain. Additionally, there was no link between academic achievement as determined by the year end exam and carious lesions or toothache (17). In a study conducted in Southern Brazil with university students, school absenteeism was assessed with the question "In the last six months, have you missed some class for dental reasons?" and 114 out of 1,850 people answered as "yes" (21).

Another study with 466 schoolchildren aged 7-8 years in the Kingdom of Bahrain highlighted that dental caries correlated with low academic achievement but not with school attendance, which is the same as our study's results (15). Another study performed in Nepal with 1,151 schoolchildren revealed that the high frequency of untreated dental caries and their repercussions (pain, infection) significantly influenced the pupils' oral health-related quality of life (13).

Studies investigating the relationship between dental status and school absenteeism/academic success in Turkey are very limited. However, when the effect of dental caries on the quality of life was examined in one study conducted in 2021, it was revealed that 3.79% of 206 pre-school children, mean age 4.09±0.97 years, were absent from school very often and 3.03% of them were frequently absent from school due to caries (22).

A tooth decay condition causes pain and anxiety and reduces the quality of life. New carious lesions, pain and extractions were the major factors contributing to dental fear and anxiety (23). Due to various negative dental treatment experiences, children with active caries may be more stressed (24). Also, nail biting is a common stress-related bad oral habit. It has been reported that people who bite their nails have more anxiety issues than those who do not (25). In addition, stress and pressure at school are among the factors which cause the development of bad oral habits such as nail biting and thumb sucking (26). In one study, it was reported that there was a relationship between nail biting and attention deficit disorder (27). In the present study, the oral habits of the patients were investigated and the relationship with their academic achievement was also examined. A statistically significant correlation was found between the nail biting and hard object biting habits of the children with their school achievement.

Study Limitations

The school achievement data obtained in this study were evaluated according to the end-of-year exam grades obtained from the families. Therefore, we have not fully measured the success of education and many factors affect this success. In addition to all these, the characteristics of schools with education centers were not evaluated, and differences between private and public schools in our country were not considered.

Conclusion

Children with lower oral health conditions were more likely to have dental pain, difficulty attending school, and a decline in academic performance. Dental caries and its repercussions have a significant impact on academic achievement. Therefore, preventing and treating dental problems and enhancing oral health may help children's academic performance in addition to their cognitive and intellectual development.

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Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of Faculty of Medicine, Ege University (dated: 20.04.2017, protocol number: 17-4/18).

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Original Article

Evaluation of Long Term Respiratory Complications in Childhood and Adolescent Cancer Survivors

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ABSTRACT

Aim: In addition to increased survival rates, systemic complications which can impair the quality of life have been seen in 25-30% of childhood and adolescent cancer cases. The respiratory system is one of the severely affected systems. We aimed to evaluate late respiratory complications and risk factors in pediatric and adolescent cancers.

Materials and Methods: We examined the pulmonary complications of 50 cancer patients and 40 control cases. We asked about environmental exposures, physical examinations performed, and pulmonary function tests (PFT) spirometry, diffusing capacity of the lungs for carbon). X-ray was performed on all patients in the patient group and on patients with indications in the control group.

Results: In the patient group, there was impairment of pulmonary function in 52%, [24% small airway disease (SAD)], 14% diffusion disorders (DD) and 14% combined disorders (CD) compared to 22.5% in the control group (p=0.007). There was a higher risk of restrictive disorder and/or SAD in those cancer patients who were diagnosed prior to 2 years of age. Additionally, there was a higher rate of SAD in those patients with soft tissue sarcomas and a higher rate of restrictive disease in those patients who had received high-dose alkylating agents. No significant PFT impairment was observed in the other patient groups.

Conclusion: There is a high incidence of respiratory impairment in childhood and adolescent cancer survivors. They need to be followed up by a multidisciplinary team and be informed about the additional risk factors which may cause lung function loss.

Keywords: Survivors of childhood cancer, pulmonary injury, pulmonary function tests

Introduction

Childhood and adolescent cancers are an increasing health problem and constitute 1-2% of all lifelong cancers. According to US data, the incidence of cancer in children and adolescents was 14.2/100,000/year in 1975, and this increased to 17.4/100,000/year in 2009.

Correspondingly, there was a notable reduction in mortality in these patients (from 5.2/100,000 to 2.4/100,000) (1). More than 1% of the young adult population are survivors of childhood cancer (2). Two-thirds of long-term survivors had at least one health problem in the late period. According to the results of the Childhood Cancer Survivors Study, for at least 5 years after cancer diagnosis,

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the cumulative death rate from cancer was 18% and deaths from lung causes were 8.8 times higher than in the normal population. The most common causes of death are tumor recurrence, secondary cancer development, cardiac toxicity, pulmonary disorders, and infections (3). Serious late respiratory complications are observed in patients treated for childhood cancer. Age at diagnosis, type of cancer, presence of respiratory system involvement, chemotherapy (CT), pulmonary radiotherapy (RT) and thoracic surgery are important factors in the development of pulmonary problems in the late period. In addition, previously known respiratory diseases, serious lung problems in the treatment process and environmental factors adversely affect the respiratory system. CT is one of the most important factors which can cause respiratory disorders (4,5). In this study, we aimed to determine respiratory problems and their risk factors in childhood cancer survivors by evaluating their pulmonary functions.

Materials and Methods

The study was approved by the Ethics Committee of Ege University Faculty of Medicine (approval date: 10.08.2011, approval no:11-6.1/11).

Fifty patients aged 7 years and older who had been in remission for at least 3 years after treatment were included in this study and evaluated for any pulmonary complications. In the control group, 40 siblings or healthy individuals in the same age range, without any history of cancer, were evaluated.

The age distribution of the patients was 10-34 years, and the control group was 11-30 years. In terms of the distribution by gender, 42% were female in the study group, and 37.5% were female in the control group. In the patient group, the median age at diagnosis was 11.5 (1-17 years), and the median age at the study time was 19.5 (10-34 years). The median age in the control group was 21 (11-30 years). The study group included 16 cases with acute leukemia, 15 with lymphoma, 10 with bone and soft tissue sarcoma, 4 with central nervous system tumors and 5 with other solid tumors. We aimed to evaluate respiratory disorders in the patients via spirometry, diffusing capacity of the lungs for carbon monoxide (DLCO) and radiological imaging (if necessary). All results were evaluated by a multidisciplinary team including a pediatric oncologist, a pulmonologist and a radiologist. The PFT parameters of the case and control groups were compared (Table I), and then the pulmonary function test (PFT) parameters were evaluated according to the diagnoses and diagnostic groups of the cases (Tables II and III) and the risk factors of the patients for restrictive disorder (RD), diffusion disorder (DD) and small airway disease (SAD) were calculated (Table IV).

Diagnostic Evaluation

The type of cancer, age at diagnosis, the presence of pulmonary involvement, the type and dose of the chemotherapeutic agents [alkylating agents ifosfamide (IFO), cyclophosphamide (CYC), bleomycin], thoracic RT, and severe pulmonary problems following surgical treatment (infections, infarction, etc.) were recorded from the follow-up files. Lung problems before and after cancer, and smoking (passive-active) were investigated. The cancer survivors were grouped into Leukemia+lymphoma patients (Group A), bone and soft tissue tumor patients (Group B), and other solid tumor patients (Group C).

PFT

PFTs were performed by the same technician with V-max spectra 22 in the pulmonary function laboratory of Ege University Faculty of Medicine, Department of Chest Diseases.

The patients rested for at least 5 minutes before the test and the test was performed in an upright position. During the test, the patient's nostrils were closed with a soft latch, all participants were required to perform the maneuvers three times and their best result was accepted for analysis.

For participants over the age of 18, spirometric tests were evaluated according to the Common Terminology Criteria for Adverse Events v3.0 criteria (6) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (7).

For those participants under 18 years of age, spirometric tests were evaluated by a pediatric pulmonologist according to their age, weight and height serıes ATS/ERS task force: standardization of lung function testing (8-12).

The classification of PFT disorders were defined as follows;

Restrictive disorder (RD): FEV1<80%, FVC<80%, FEV1/FVC>70,

Small airway disorder (SAD): FEF_{25-75}<80%,

Diffusion disorder (DD): DLCO<75%,

Obstructive disorder (OD): FEV1<80%, FVC; N/low, FEV1/FVC<70

Statistical Analysis

Statistical analyses were performed using IBM SPSS version 24.0 for Windows. In comparison of two independent groups, the t-test was used for parametric test assumptions and the Mann-Whitney U test was used for

Table I. Comparison of case group and control group respiratory function tests

PFT	Groups	Mean ± SD (minimum-maximum)	p-value
FVC	Patients	96.46±14.3 (53-128)	0.015
	Control	103.40±11.7 (81-125)	
FEV1	Patients	99.10±14.1 (55-135)	0.103
	Control	103.55±10.7 (79-131)	
FEV1/FVC	Patients	87.54±5.8 (71-99)	0.107
	Control	85.52±5.8 (70-98)	
FEF_{25-75}	Patients	87.12±21.5 (43-141)	0.245
	Control	92.20±19 (48-141)	
DLCO	Patients	93.91±18.7 (52-132)	0.322
	Control	97.82±17.8	

SD: Standard deviation, DLCO: Diffusing capacity of the lungs for carbon, PFT: Pulmonary function test

Table II. Evaluation of respiratory function tests according to the diagnoses of the cases

	FVC		FEV1		FEV1/FVC		FEF_{25-75}		DLCO	
Group	Mean-SD	p-value	Mean-SD	p-value	Mean-SD	p-value	Mean-SD	p-value	Mean-SD	p-value
B (n=10)	96.7 (10.1)	0.760	94.9 (10.2)	0.357	84.9 (6.4)	0.092	78.7 (20.7)	0.399	85.8 (11.9)	0.522
C (n=9)	95 (13.7)		101.2 (18.1)		89.8 (5.7)		87.3 (22.7)		81.1 (17.2)	
B (n=10)	96.7 (10.1)	0.984	94.9 (10.2)	0.314	84.9 (6.4)	0.184	78.7 (20.7)	0.160	85.8 (11.9)	0.05
A (n=31)	96.8 (15.8)		99.8 (14.0)		87.7 (5.4)		89.7 (21.6)		99.7 (18.3)	
C (n=9)	95 (13.7)	0.759	101.2 (18.1)	0.809	89.8 (5.7)	0.306	87.3 (22.7)	0.768	81.1 (17.2)	0.01
A (n=31)	96.8 (15.8)		99.8 (14.0)		87.7 (5.4)		89.7 (21.6)		99.7 (18.3)	

Table III. Evaluation of pulmonary function tests by diagnostic groups

	Group A	Group B	Group C	p-value
FVC	96.8	96.7	95	0.967
FEV1	99.8	94.9	101.2	0.584
FEV1/FVC	87.7	84.9	89.8	0.229
$FEF_{(25-75)}$	89.7	78.7	87.3	0.345
DLCO	99.7	85.8	81.1	0.014

*Group A (Leukemia and lymphoma group). Group B (Bone and Soft Tissue group). Group C: (The other group)

Table IV. Evaluation of risk factors of patients in terms of RD, DD, and SAD (odds ratio and 95% confidence interval)

Variables	RD	DD	SAD
Age (<2 years)	2.5 (0.22-28.81)	-	2.71 (0.41-18.00)
Gender (female)	2.25 (0.34-14.83)	2 (0.46-8.65)	1.00 (0.31-3.20)
Diagnosis (Group B)	2.3 (0.34-15.95)	0.41 (0.04-3.79)	3.11 (0.74-12.98)
Time after treatment*	0.77 (0.07-7.66)	0.62 (0.14-2.72)	0.76 (0.19-3.00)
Pulmonary disorders	0.58 (0.07-4.55)	1.25 (0.27-5.76)	0.75 (0.23-2.43)
Alkylating	4.77 (0.37-61.06)	5.28 (0.63-44.03)	5.62 (0.54-58.57)

* >5 years compared to <5 years
RD: Restrictive disorder, DD: Diffusion disorder, SAD: Small airway disease

those which were not provided. In the comparison of more than two groups in terms of numerical variables; The One-Way ANOVA test was used for normal distribution and the Kruskal-Wallis test was used for non-normal distributions. The difference between groups in terms of categorical variables was examined by Pearson or Fisher's exact test. The significance level was taken to be $p<0.05$.

Results

We observed respiratory impairment in 52% of the cancer survivors group (24% SAD, 14% DD and 14% combined disorders) and 22.5% in the control group (17.5% SAD, 2.5% DD and 2.5% combined disorders) (p=0.007). Compared to the control group, FVC was found to be significantly lower in the cancer survivors (p=0.015) (Table I).

FEV1/FVC values were impaired in those patients with pulmonary involvement at the time of diagnosis or during their follow-up (p=0.037). No deterioration was detected in the other PFT parameters. Seven Hodgkin lymphoma (HL) patients with impaired PFTs received an average of 30 Gy RT and pulmonary/mediastinal involvement was observed in these patients. In 7 patients with leukemia who had severe lung infections during their treatment, there was no statistically significant difference in any of the PFT parameters.

The cancer survivors were grouped into Leukemia+lymphoma patients (Group A), bone and soft tissue tumor patients (Group B), and other solid tumor patients (Group C). PFT disorders in these groups were compared. SAD was observed more in Group B (60%) but it was not significant. DLCO was lower in Groups B and C compared to Group A (p=0.014). No other differences were observed among the three groups (Tables II and III).

The mean of FEF25-75 under 2 years old was 67.2% and for over 2 years old, it was 89.3% (p=0.027).

PFT values were found to be lower in patients more than 5 years after the end of their treatment compared to patients less than 5 years, but this was not statistically significant. No significant difference was observed when the PFTs of the patients in the follow-up period of less than 5 years, 5-10 years and more than 10 years were compared. Although the change in DLCO was observed to be more pronounced, this change was not found to be significant (p=0.468) (Figure 1).

Alkylating agents were given to 44 patients. CYC (1-16 gr/m^2) was given to 22 patients, IFO (4-54 gr/m^2) to 10 patients, and their combination (IFO+CYC) to 14 patients. We observed that alkylating agents increased the risk of RD by 4.7 times [odds ratio (OR): 0.37-61.06] and SAD by 5.6 times (OR: 0.54-58.57), but these were not found to be statistically significant. RD was determined to be similar in all three drug groups (9%, 10%, 7%, respectively).

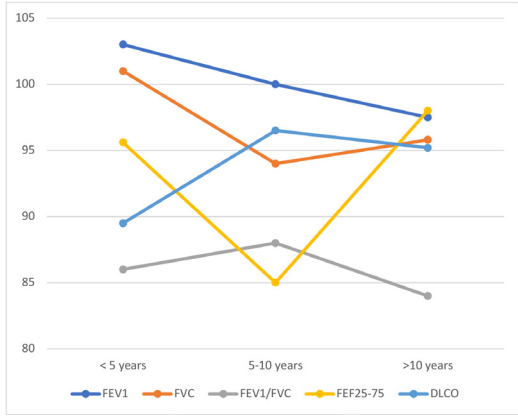

Figure 1. PFT disorder according to the post-treatment follow-up processes

There was a non-significant trend for a higher risk of developing RD and/or DD in females (Table IV).

Discussion

Survival rates in childhood and adolescence cancers have increased significantly in the last 20 years. It is known that 75% of surviving patients face at least one health problem, and 25% have serious complications which impair their quality of life (3,5). An important part of these complications is related to the respiratory system. Age, thoracic involvement, time elapsed after treatment, treatment modalities used (CT, thoracic RT and/or surgery), pre-existing respiratory disorders, active-passive smoking and gender have been reported to be some of the risk factors associated with respiratory complications (3).

An increase in respiratory disorders is expected in cancer survivors in the late period. In a series of 27 cases with HL, 48% had respiratory problems during a follow-up period of 76 months (13). Miller et al. (14) found low TLC levels in 48% of the patients in the spirometric evaluation of 29 patients. Respiratory impairment was observed in 43% of patients with malignant brain disease (15). Similarly, in a study of 5,760 ALL patients, there was a 4.2-fold increased risk of lung fibrosis compared to the normal population (16). In addition, other similar studies have reported that respiratory complications in children with cancer vary between 7.8% and 65% (14,17,18). In our study, we observed a higher rate of respiratory impairment in cancer survivors than in the control group.

Generally, pulmonary function disorders are classified into groups (RD, SAD, DD, OD). In other studies, it was observed that RD was between 7.5-87% and DD was between 10-40%

(13,15,19-21). In our cases, SAD was 24%, DD was 14%, and 14% were combined disorder.

It is known that diagnosis at a young age increases the susceptibility to pulmonary dysfunction in cancer survivors. O'Driscoll et al. (22) showed that the risk of severe fibrosis leading to death in patients diagnosed before 6 years of age increased significantly. In another study of 22 NHL and 19 HL case groups, the mean age at diagnosis was shown to be a significant risk factor for low total pulmonary capacity (23). In a pulmonary toxicity study, TLC was found to be decreased in those patients diagnosed before 3 years of age (14). In another study, lung toxicity was found to be higher in children diagnosed with ALL at an early age (23). In our study, for those under 2 years of age, the risk of RD increased by 2.5 times (OR: 0.22-28.81), and SAD by 2.71 times (OR: 0.41-18.00). Although the FVC and FEV1 values were lower, this did not reach statistical significance.

It has been shown that respiratory functions are affected in the follow-up process of child and adolescent cancer survivors (4). O'Driscoll et al. (22) reported that FVC decreased in the first 3 years after treatment in patients with CNS, and there was no significant change in FVC in the 10-year follow-up. Bossi et al. (13) reported that there was no change in PFT during the post-treatment follow-up. In our case group, a decrease in FEV1, FVC, FEF_{25-75} values were observed in the 5-10 year follow-up subgroup, followed by a partial improvement beyond ten years. This improvement after 10 years may be due to the fact that children reach adulthood, increase in their physical activity and move away from the effects of their treatment.

Studies suggest that CT, especially alkylating, bleomycin, and methotrexate, may cause respiratory complications. Mertens et al. (4) reported that the risk of recurrent lung infection and chronic cough is higher in cancer survivors, especially in alkylating users. In a similar study, it was reported that the risk of RD development increased 1.5 times and that the risk of DD increased 1.25 times in HD-CYC users (24). Another study showed that the use of another alkylating agent HD-IFO increased toxicity (25). In our study, RD and DD were observed in 9 and 22% in CYC and 7 and 14% in CYC+IFO users, while no RD developed in patients who received IFO monotherapy. IFO treatment was not associated with RD and DD.

It has been shown in many studies that RT applied to the thorax can cause late respiratory complications (5,26). It has been reported that respiratory complications occur at a rate of 5-15% in child and adolescent cancer survivors exposed to total RT>30 Gy (27). Many studies on children and adolescents undergoing thoracic RT have shown that these patients develop pulmonary fibrosis and PFT impairment (22-75%) (4,28-31). All three patients with HL-related thoracic involvement who received RT in our study developed respiratory impairment.

In a cohort study of childhood cancer survivors (606 RMS cases and 3,701 sibling controls), 3% of RMS cases (due to lung RT) were shown to have pulmonary fibrosis (32). In addition, in another study, PFT disorders were found in 19% of patients with thoracic involvement neuroblastoma (which developed as RD in half and OD in the other half) (33).

In the results of our patient groups, FEF 25-75 values were found to be lower in Group B patients. These results showed that lung tumor involvement, thoracic surgery and the use of RT and HD alkylating agents were effective in this group. On the other hand, DD was more frequent in Group C. The mean PFT values in those patients with leukemia-lymphoma were within normal limits and no significant change was observed.

Late term respiratory complications have been reported to develop more frequently in girls (19,24). There was also 2 times and 2.5 times higher risks of developing DD and RD, respectively, in this study, although this trend did not reach statistical significance, possibly due to relatively low number of patients.

Late effects on the respiratory system are manifested by various clinical symptoms and PFT disorders, and they may have serious consequences which lead to secondary lung cancer and/or death in the following years (4,34). In our group, secondary lung malignancy and fatal respiratory complications were not observed during a follow-up period of 3-21.6 years.

Study Limitations

The heterogeneity of the diagnoses of the case group in our study led to differences in terms of treatment modalities. However, the cases were grouped according to cancer types and/or the similar treatment modalities applied, the results were examined and the results obtained were generally parallel to other studies reported to date.

Conclusion

In our study, the rate of impairment of PFTs was found to be 52% and age at diagnosis, gender, cancer type, the presence of lung involvement, and the treatment modalities contributed to the development of PFT disorders. It was observed that especially being diagnosed under 2 years of age increased the risk of RD and SAD. Also, bone and soft tissue tumors increased the risk of SAD, and additionally, the use of HD alkylating agents increased the risk of RD, DD and SAD.

As a result, childhood and adolescent survivors have to be followed up with a multidisciplinary approach.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Ege University Faculty of Medicine (approval date: 10.08.2011, approval no:11-6.1/11).

Informed Consent: Informed consent was obtained from the parents/legal guardians of the patients.

Authorship Contributions

Medical Practices: F.E., N.Ç., E.D., A.S., H.A., F.G., Concept: F.E., N.Ç., F.G., Design: F.E., N.Ç., Data Collection or Processing: F.E., N.Ç., Analysis or Interpretation: F.E., N.Ç., E.D., A.S., H.A., F.G., Literature Search: F.E., N.Ç., E.D., Writing: F.E., N.Ç., E.D., A.S., H.A., F.G.

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Original Article

The Prophylaxis of Febrile Convulsions in Childhood: Secular Trends in the Last Decade (2007-2008 versus 2017-2018)

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ABSTRACT

Aim: To analyze trends in the prophylaxis of febrile convulsions (FC) in childhood by comparing two cohorts from the previous two decades (2007-2008 versus 2017-2018).

Materials and Methods: The cohort consisted of 272 children with FC who were followed up during the 2007-2008 (n=105) and 2017-2018 (n=167) periods in Ege University Faculty of Medicine Children's Hospital. The following clinical parameters were analyzed: demographic data, FC types, prophylaxis types, selected anti-seizure medications (ASM), recurrence risk factors, and electroencephalography (EEG) characteristics.

Results: We defined two secular trends for the prophylaxis of FC in children in the last decade: (1) a reduced rate of FC prophylaxis (22.1%) in the period of 2017-2018 compared with a rate of 63.8% in 2007-2008, $p<0.01$, (2) no impact of recurrence risk factors for the initiation of prophylaxis for complex FC in the last decade ($p=0.028$). The mean number of previous seizures at the initiation of the ASM prophylaxis increased from 2.8±1.13 to 3.4±2.00 for simple FC and from 1.9±0.24 to 3.1±0.31 for complex FC ($p<0.01$) in the period of 2017-2018.

Conclusion: Prophylaxis rates were determined to be lower in the last decade in children with FC. There was no impact of recurrence risk factors for the initiation of prophylaxis in children with simple or complex FC.

Keywords: Febrile convulsion, ASM prophylaxis, febrile convulsion recurrence risk factors

Introduction

Febrile convulsions (FC) are common in childhood, with a risk of seizure recurrence of 33% (25-50) and also a low risk of developing epilepsy (1,2). FC recur in almost 1/3 of cases, and 10% of cases experience more than three seizures in a lifetime. The decision to initiate anti-seizure medication (ASM) prophylaxis and the prognosis is essential for the clinician in FC. In the past years, there have been certain recommendations on initiating prophylaxis of FC with ASM regarding the number of previous seizures and the risk factors of febrile seizure recurrence. In more recent years, the prophylaxis of simple FC (SFC) has not been recommended regardless of recurrence risk factors and the number of previous seizures due to the potential adverse effects of the drug (3-5). Children with complex FC are considered on a case by case basis for ASM prophylaxis.

The Japanese Society of Child Neurology (2015) suggested two types prophylaxis based on the certain criteria; (1)

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intermittent and (2) continuous prophylaxis to manage FC cases and they do not recommend prophylaxis for one or two SFC attacks without recurrence risk factors (5).

1) The initiation criteria for the use of intermittent prophylactic diazepam are as follows:

- History of prolonged FC lasting ≥15 min
- History of recurrent FC with a short interval in between (2 FC within 12 hours, >3 FC within 6 months)
- History of ≥2 FC with ≥2 of the risk factors stated below:
- Focal seizure, recurrent seizures within 24 hours
- Presence of developmental delay and neurological abnormality
- Family history of epilepsy on FC
- Age of patient <12 months
- Febrile seizure within 1 hour after the onset of fever
- FC with body temperature <38 °C.

2) Continuous use of phenobarbital, sodium valproate, and levetiracetam recommended after pediatric neurology consultation with the criteria given below:

• History of prolonged FC lasting ≥15 minutes without diazepam prophylaxis due to unawareness of fever before FC

• History of protracted FC lasting ≥15 minutes despite prophylactic diazepam treatment at the appropriate time and the right dose

• History of >2 repeated convulsions when body temperature <38 °C.

The drugs preferred for intermittent treatment can be rectal diazepam or oral clobazam. Oral sodium valproate, phenobarbital, or levetiracetam have been reported in continuous prophylactic treatment depending on the children's clinical features (6).

The aim of this study was to analyze the trends in the prophylaxis of FC in the new era (period: 2017-2018) and to include a comparison with the previous decade (period: 2007-2008).

Materials and Methods

Study Design

From the archive of the Child Neurology Department at Ege University Hospital, 272 children with FC were included in this study from two different follow-up periods (2007-2008 and 2017-2018). The inclusion criteria were children aged 6-60 months without any history of afebrile convulsion and with a history of convulsion during a febrile disease without significant CNS infection or acute metabolic dysfunction. The exclusion criteria were having a diagnosis of Dravet syndrome or generalized epilepsy with febrile seizure plus (GEFS+).

The demographic features of the patients were recorded; seizure parameters such as duration (≤15 min and >15 min), type (focal, generalized), number of seizures in the same disease period; risk factors for FC recurrence, age at first FC, family history of FC, body temperature when FC occurred (≥39 °C vs. <39 °C), time passed between the onset of fever and convulsion occurrence; EEG findings and the presence of prophylaxis of FC were registered according to the children's records.

Based on the previously defined departmental FC recurrence risk factors, we evaluated the following four predominant factors as follows: first convulsion before the age of one year, family history of FC, FC occurrence with body temperature <39 °C via rectal measurement, and FC onset within the first hours of fever onset (1).

The ratio of initiating prophylaxis for FC, the FC recurrence risk factors, and the demographic characteristics which could be determined at the initiation of the ASM prophylaxis were compared between the two groups.

Statistical Analysis

The study data was evaluated via the SPSS 22.0 Windows version of the SPSS statistical package (SPSS, Chicago, IL, USA). Variables displaying a parametric distribution were analyzed using the independent t-test, and the results are presented as mean and standard deviation. Variables indicating a non-parametric distribution were compared via the Mann-Whitney U test, and the results are presented as median (minimum-maximum). Categorical variables were analyzed using the chi-squared test and Fisher's exact test, depending on the sample size. The results are given as number and percentage. The level of statistical significance was set at $p<0.05$.

The Ege University Hospital Ethics Committee granted ethics committee approval (project no: 22-6.1T/34, date: 23.06.2020).

Results

Demographics

A total of 272 children were admitted into this study. The male/female ratio was 1.47/1. The mean age of the sample group was 19.9±12.5 (6-110) months. Within the study group, 68.4% had simple FC, and 31.6% had complex FC. Febrile status epilepticus (>30 minutes of seizure duration)

was determined in 16 patients (5.9%). The percentages of family history of FC and epilepsy were 52.6% and 14%, respectively. All children had electroencephalography (EEG). The EEG analyses were normal in 83.5% of the study group (Table I). When the cases were grouped regarding their follow-up periods as either 2007-2008 or 2017-2018, there was no statistical significance found between the two groups in terms of age, sex, seizure type, diagnosis of status epilepticus, family history of FC, or the total number of risk factors for FC recurrence (p>0.05) (Table II). However, there were statistically significant differences between the two group for prophylaxis rate, type and drug used (Table II). The rate of prophylaxis was significantly reduced in the second period (2017-2018).

Prophylaxis with ASM

ASM prophylaxis was initiated for 38.2% (104/272) of all study groups; intermittent and continuous prophylaxis in 28.8% and 71.2% of the children, respectively. The intermittent rectal diazepam prophylaxis rate significantly reduced in the second period (p=0.001) (Table II). Valproic acid was the most preferred drug for prophylaxis in both periods. However, levetiracetam became an alternative drug for prophylaxis (p=0.001).

The ratio of prophylaxis for FC cases was 63.8% (CFC: 38.9% and SFC: 61.1%) in the 2007-2008 period and 22.1% (CFC: 59.4% and SFC: 40.6%) in the 2017-2018 period (Table III). Our ratio of initiating prophylaxis for FC with ASM decreased significantly over the years, and ASM prophylaxis was preferred for CFC cases more than SFC (p<0.01).

Table IV presents the comparison of the two cohorts (2007-2008 versus 2017-2018) on FC prophylaxis regarding their follow-up periods. The mean number of total seizures increased from 2.8±1.13 to 3.4±2 for SFC (p=0.254) and from 1.9±0.24 to 3.1±0.31 for CFC (p<0.05) in the second period. Children with SFC on ASM prophylaxis had more normal EEGs in 2007-2008 when compared to the period of 2017-2018. However, there was no significant EEG difference between the two periods of those children with CFC on ASM.

Risk factors analysis for prophylaxis

The impact of FC recurrence risk factors for the initiation of prophylaxis was compared for the two periods. In the second period (2017-2018), the number of risk factors was significantly higher in those children who did not initiate ASM prophylaxis for complex FC (p=0.028) (Table V).

Table I. Demographic data of the study cohort

Follow-up period, n (%)	2007-2008	105 (38.6)
	2017-2018	167 (61.4)
Age at first seizure, month (mean ± SD)		19.9±12.5
Gender, n (%)	Female	110 (40.4)
	Male	162 (59.6)
Febrile convulsions type, n (%)	Simple	186 (68.3)
	Complex	86 (31.4)
Presence of febrile status epilepticus, n (%)		16 (5.9)
Recurrence risk factors	First convulsion before the age of one year	83 (30.5)
	Family history of febrile convulsion	143 (52.6)
	Febrile convulsion occurrence with body temperature <39 ºC	28 (10.3)
	Febrile convulsion onset within the first hours of fever onset	37 (9.9)
Electroencephalography	Normal	227 (83.5)
	Focal intermittent slow waves	4 (1.5)
	Paroxysmal epileptiform discharges	35 (12.8)
	Generalized epileptiform discharges	6 (2.2)
Prophylaxis rate, n (%)		104 (38.2)
Prophylaxis type, n (%)	Intermittent (rectal diazepam)	30 (28.8)
	Continuous	74 (71.2)
Seizure after prophylaxis, n (%)		20 (19.2)

Table II. Demographic data comparison of the two study groups with febrile convulsions (n=272)				
		Follow-up period		
		I: 2007-2008 (n=105)	**II: 2017-2018 (n=167)**	**p-value**
Age at first seizure, month (mean ± SD)		20.76±11.6	19.5±13.04	0.561*
Gender, n (%)	Female	41 (39)	69 (41.3)	0.826$^{\Delta}$
	Male	64 (61)	98 (58.6)	
Febrile convulsions type, n (%)	Simple	73 (69.5)	113 (67.6)	0.685$^{\Delta}$
	Complex	32 (30.5)	54 (32.4)	
Presence of febrile status epilepticus, n (%)		6 (5.7)	10 (6)	0.901$^{\Delta}$
Family history of febrile seizure, n (%)		50 (47.1)	93 (55.6)	0.154$^{\Delta}$
Recurrence risk factors	None	16 (15.2)	16 (9.6)	0.086$^{\Delta}$
	1-2 risk	79 (75.3)	124 (74.2)	
	3 risks	10 (9.5)	27 (16.2)	
Prophylaxis rate; n (%)		67 (63.8)	37 (22.1)	**0.001**$^{\Delta}$
Prophylaxis type, n (%)	Intermittent (rectal diazepam)	26 (38.8)	4 (10.8)	**0.001**$^{+}$
	Continuous	41 (61.1)	33 (89.1)	
Drug used for continuous prophylaxis, n (%)	Phenobarbital	5 (12.2)	5 (15.2)	**0.001**$^{\Delta}$
	Valproic acid	36 (87.8)	19 (57.6)	
	Levetiracetam	0	9 (27.2)	

*Independent t-test, $^{\Delta}$Chi-squared test, +Fisher's exact test

Table III. Prophylaxis of febrile convulsions				
Follow-up period	**Febrile convulsion type**	**Prophylaxis (+) n, (%)**	**Prophylaxis (-) n, (%)**	**p-value**
I: 2007-2008 (n=105)	Simple Complex Total	41 (61.1) 26 (38.9) 67 (63.8)	31 (81.5) 7 (18.5) 38 (36.1)	**0.003**$^{\Delta}$
II: 2017-2018 (n=167)	Simple Complex Total	15 (40.6) 22 (59.4) 37 (22.1)	99 (76.2) 31 (23.8) 130 (77.9)	**0.004**$^{\Delta}$

$^{\Delta}$Chi-squared test

Discussion

In recent years, prophylaxis of FC in children is not preferred because of the adverse effects of the drugs and the benign nature of the seizures (2). The most rational use of prophylactic treatment in children with FC is to prevent prolonged seizures. In this study, we defined two secular trends regarding the prophylaxis of FC in children: (1) a significantly reduced rate of FC prophylaxis (22.1%) and (2) no significant impact of recurrence risk factors on the initiation of prophylaxis in complex FC in the recent period.

Before 2008, the recommendation for the initiation of prophylaxis for FS was as follows:

• If there was no risk factor for FC recurrence, the presence of three seizures for boys and the presence of two seizures for girls,

• If there was only one risk factor, the presence of two seizures for either sex was an indication for prophylaxis.

• If there were two or more risk factors, immediate prophylaxis was recommended.

Since 2008, the American Academy of Pediatrics has not recommended prophylaxis for SFC, regardless of risk factors and the number of FC recurrences (4). The Japanese Society of Pediatric Neurology (2015) recommended

Table IV. Demographic data comparison of the two groups on febrile convulsion prophylaxis (n=104/272, 38.3%)

		Simple febrile convulsion		p-value	Complex febrile convulsion		p-value
Follow-up years		**I: 2007-2008**	**II: 2017-2018**		**I: 2007-2008**	**II: 2017-2018**	
Gender n, (%)	Male Female	27 (65.8) 14 (34.2)	10 (66.6) 5 (33.4)	0.609$^{\Delta}$	19 (60.2) 7 (39.8)	11 (50) 11 (50)	0.100$^{\Delta}$
Number of seizures		2.8±1.13	3.4±2	0.254*	1.9±0.24	3.1±0.31	**0.04***
Age at first febrile seizure (month)		16±3.42	14 ±9.48	0.867*	21±2.7	14.6±1.8	**0.047***
Electroencephalography n, (%)	Normal Abnormal	31 (75.7) 10 (24.3)	7 (46.6) 8 (53.4)	**0.040**$^{\Delta}$	14 (42.3) 11 (53.8)	14 (27.3) 8 (72.7)	0.595$^{\Delta}$

*Independent t-test, $^{\Delta}$Chi-squared test

Table V. The impact of recurrence risk factors on the initiation of febrile convulsion prophylaxis

			Follow-up periods		p-value
			I: 2007-2008	**II: 2017-2018**	
Simple febrile convulsion n, (%)	**Prophylaxis (+)**	No-risk 1-2 risks 3 risks	4 (9.8) 25 (60.9) 12 (29.3)	1 (6.7) 10 (66.7) 4 (26.7)	0.91
	Prophylaxis (-)	No-risk 1-2 risks 3 risks	3 (9.7) 22 (71) 6 (19.4)	17 (17.1) 75 (75.8) 7 (7.1)	0.10
Complex febrile convulsion n, (%)	**Prophylaxis (+)**	No-risk 1-2 risks 3 risks	2 (7.7) 19 (73.1) 5 (14.2)	0 20 (90.9) 2 (9.1)	0.48
	Prophylaxis (-)	No-risk 1-2 risks 3 risks	3 (42.9) 4 (57.1) 0	2 (6.5) 28 (90.3) 1 (3.2)	**0.028**

$^{\Delta}$Chi-squared test

restricted guidelines for the prophylaxis of FC in children (5). Today, there is no clear consensus on the initiation of FC prophylaxis.

In this study, we determined a significantly reduced rate (22.1%) of prophylaxis in children with FC in the last decade (2017-2018). In a study conducted at the same time as our study (2017-2018), it was reported that 43.3% of all children used intermittent or continuous prophylaxis for FC, with 24.7% for SFC and 89.1% for CFC. Another study conducted between 2002 and 2006 revealed the prophylaxis rate to be 64.8%, similar to the rate (63.8%) of the 2007-2008 period in our study (7-11).

Risk factors for FC recurrence have been reported in previous studies (1,2,7). However, there has been no clinical study evaluating the impact of risk recurrence factors for initiating ASM prophylaxis in children with simple or complex FC. Following a single simple FC, the probability of recurrence generally ranges between 30 and 40%. In the presence of one or two risk variables, the recurrence frequency rises to 25–50% from 10% in those children without risk factors. If there are three or more risk factors, it may rise even further to 50-100% (8). In a prospective study, a two-year risk of recurrence in children with a single febrile seizure was reported at 14%, 24%, 32%, 63%, and 75% in the presence of 0, 1, 2, 3, or 4 risk factors, respectively. No difference was reported in the risk of recurrence based on whether the initial febrile seizure was simple or complex (9). The prognosis of a child with FC who was neurologically normal prior to their first FC is unaffected by its recurrence (10). Therefore, the need for any prophylaxis for FC should be carefully considered on a case-by-case basis. In the present study, we found no significant impact of recurrence risk factors on the initiation of prophylaxis in both types of FC. We also determined that the mean number of seizure recurrences without prophylaxis increased in simple and complex FC sample groups, and that prophylaxis decisions were made independently of the risk factors for FC recurrence.

Two meta-analyses revealed that intermittent oral or rectal diazepam, phenobarbital, phenytoin sodium, sodium valproate, ibuprofen, diclofenac sodium, or paracetamol do not prevent recurrent FC (12,13). In subsequent meta-analyses, a significant reduction of recurrent febrile seizures with intermittent diazepam and phenobarbital versus placebo or no treatment was reported (6,14). However, in the meta-analysis presented in 2017 and 2021, Cochrane drew attention to the drugs' adverse effects, even if prophylaxis prevents seizure recurrence. At the end of their meta-analysis, they made the following suggestions: Children with febrile seizures are not recommended to receive continuous or intermittent anti-seizure or antipyretic treatment. Parents and families should be provided with contact information for medical services, as well as information about recurrence, first aid, and the phenomena's benign nature (6,15). If prophylactic treatment is to be initiated, intermittent rectal diazepam treatment has been highlighted as the first step in the Japanese Society of Child Neurology recommendations, and recent reviews (5,16). Conversely, our study's rate of intermittent prophylaxis decreased in the second period of the study cohort. In addition, in the 2021 Cochrane meta-analysis, it was stated that intermittent oral levetiracetam and clobazam treatment reduced the frequency of FC compared to a placebo (15).

There is no proof that EEG findings obtained at the presentation of a straightforward FC or during the next month may be used to predict the likelihood of either a future FC recurrence or the onset of epilepsy within the next two years. Furthermore, there is no proof that any interventions based on the EEG results will change the child's prognosis of developing epilepsy in later life (10). For this reason, EEG is not recommended for children with normal neuromotor development or simple FC. However, if EEG is planned, it should be carried out 7-14 days after FC to eliminate the possibility of false evaluation which may be caused by infection or fever (17,18). On the other hand, after a CFS, a routine EEG should be considered. An EEG recorded on the day of or soon after the seizure may help to clarify whether there is any doubt that the event was a seizure. Otherwise, there is conflicting information about how well the detection time and characteristics of EEG abnormalities may predict future febrile or afebrile seizures. However, it has been suggested that getting an EEG within seven days may enhance the chances of identifying abnormalities. Furthermore, there has been no conclusive proof that specific EEG abnormalities might indicate the likelihood of developing epilepsy; instead, the persistence of EEG abnormalities is regarded to have a more substantial predictive power (19). In a retrospective analysis of 113 cases with their first FC, EEG findings were grouped as pseudo-petit mal discharge, epileptiform discharge, and normal. It was reported that FC recurrence risk doubles with an abnormal EEG (20). In another study from Turkey, EEGs were performed on 22.5% of FC cases (10.7% of SFC and 75% of CFC). Thirty-five percent of the first EEG results obtained were normal, while 98.1% of the last EEG results were normal. They concluded that EEG could not be used as a guide for the follow-up or treatment of FC (2). Although we did not consider EEG abnormalities while initiating prophylaxis for FC, our retrospectively analyzed data showed that, in the 2017-2018 period, children with a history of SFC tended to have a higher ratio of abnormal EEG findings. Nevertheless, EEG abnormalities in simple FC had little influence on our decision to initiate FC prophylaxis with ASM.

In our study, the male/female ratio was 1.47, similar to other studies carried out in our clinic and country (1,7). In a study including 1,385 FC cases, 1,245 (89.8 %) were reported as SFC and 140 (10.2%) as CFC. In this study, both children who were followed by the pediatric neurology clinic and those who applied to the emergency care unit were evaluated (21). In another study with a student population, the total percentile of CFC was reported as 18.4% (2). In another study in which only children followed in the pediatric neurology clinic were included, the SFC rate was 71.6%, and the CFC rate was 28.4%, similar to our cohort, as the percentages of simple and complex FC in our study were 68% and 32%, respectively (11).

Study Limitations

The small sample size and absence of a standard departmental protocol to initiate prophylaxis for FC were the main limitations of our study. Additionally, this paper could not evaluate the odds ratio of risk factors which we believed to affect the decision on the initiation of prophylaxis. Also, our study was designed as a retrospective comparative study for two different follow-up periods. We therefore could not perform a comparison of the prophylaxis sub-group in terms of their long-term recurrence ratios and their epilepsy risk ratios.

Conclusion

Prophylaxis for FC has significantly decreased during the previous decade, with a current rate of 21%. Despite the guidelines' recommendations, the rate of prophylaxis with ASM is still high in children with FC. Validated scoring models, including predominant risk factors, are needed to determine those children with FC who require prophylaxis.

Ethics

Ethics Committee Approval: The Ege University Hospital Ethics Committee granted ethics committee approval (project no: 22-6.1T/34, date: 23.06.2020).

Informed Consent: Our study was designed as a retrospective comparative study for two different follow-up periods.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Design: Data Collection or Processing: Analysis or Interpretation: Literature Search: Writing: All authors have contributed equally.

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

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Original Article

Factors Associated with the Development of Adrenal Insufficiency in Patients with Juvenile Idiopathic Arthritis Who Received Systemic Corticosteroids

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ABSTRACT

Aim: In juvenile idiopathic arthritis (JIA), systemic corticosteroids are reserved for cases with serious organ involvement, those with macrophage activation syndrome, and in the presence of high disease activity in oligoarticular and polyarticular JIA. However, systemic steroids may lead to serious side effects linked to adrenal insufficiency (AI). This study aimed to investigate factors related to AI in children with JIA who received systemic steroids.

Materials and Methods: Twenty-five children with AI (serum cortisol <18 µg/dL 30 minutes after adrenocorticotropic hormon stimulation) and 25 children without AI were included in this study. The subjects' characteristics, type of JIA, arthritis location, laboratory measurements, and number of joints involved were recorded. The type of glucocorticoid administered, the treatment protocol, and the cumulative steroid dose were recorded. The primary endpoint was the difference in clinical characteristics, laboratory measurements and systemic corticosteroid dose in those children with or without AI.

Results: The median cumulative steroid dose was significantly higher in those patients with AI compared to those without [2,500 (1,370-4,400) mg vs. 963 (650-2,500) mg, p=0.010]. Patients with oligoarticular JIA had a 6.7-fold lower risk of AI compared to those with other JIA types [odds ratio (OR): 0.149, 95% confidence interval (CI): 0.035-0.643, p=0.011]. Those patients with higher cumulative steroid doses (>1,000 mg) had a 7.5-fold higher risk of AI than those with lower doses (OR: 7,500, 95% CI: 1,634-34,416, p=0.010).

Conclusion: Our findings show that non-oligoarticular JIA and high cumulative steroid doses are predictive for AI development in this patient subset; thus, systemic corticosteroids should be reserved for more aggressive JIA types and the cumulative dose should be limited to 1,000 mg.

Keywords: Juvenile idiopathic arthritis, systemic corticosteroids, adrenal insufficiency

Introduction

Juvenile idiopathic arthritis (JIA) is described as persistent arthritis of unknown etiology present for at least 6 weeks. In JIA, there is often multi-organ involvement in addition to arthritis, including the eyes, skin, and internal organs (1,2). Although its etiology is unclear, several factors

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such as genetic predisposition, infections, and trauma may contribute to JIA development. Abnormal activation of T-cells, B-cells, natural killer cells, dendritic cells, macrophages, neutrophils, and the resultant increase in pro-inflammatory mediators are considered to cause JIA and are also implicated in joint involvement and systemic complications (3,4).

Treatment options include non-steroidal anti-inflammatory drugs (NSAIDs), methotrexate or sulfasalazine as a disease-modifying anti-rheumatic drug, systemic or intra-articular corticosteroids, and biologic agents (5-8). Corticosteroids reduce the activation and proliferation of immune cells via cellular and transcriptional alterations, resulting in reduced production of pro-inflammatory cytokines including interleukin (IL) 1 and IL6 (9,10). In JIA, systemic corticosteroids are reserved for systemic JIA with serious organ involvement (such as myocarditis and pericarditis), in the presence of associated macrophage activation syndrome, and when disease activity is high in oligoarticular and polyarticular JIA. However, systemic corticosteroids may lead to serious complications including infections, myopathy, neuropsychiatric symptoms, osteoporosis, obesity, insulin resistance, gastric intolerance, cataract, glaucoma, and/or adrenal insufficiency (AI). Particularly, AI has been associated with fatigue, growth failure, obesity, hypertension, hyperglycemia, osteoporosis and muscle weakness. Given the likelihood of such serious complications, identifying the factors associated with AI development in patients with JIA receiving systemic corticosteroids is important.

As such, this study aimed to investigate those factors independently associated with AI in children receiving systemic corticosteroids for JIA.

Materials and Methods

This retrospective study was conducted at the Department of Pediatrics of İstanbul Medeniyet University Göztepe Training and Research Hospital, İstanbul, Turkey. Data regarding children with JIA diagnosed according to the criteria established by the International League of Associations for Rheumatology (ILAR) who were <18 years of age and were treated with glucocorticoids between 2007 and 2013 were retrieved from their patient charts and the institutional digital database (11). From these children, those who received low dose (1 mcg) adrenocorticotropic hormon (ACTH) tests for the assessment of the pituitary-adrenal axis were included in the final analyses. Children with underlying chronic disorders, particularly those with conditions predisposing to infectious diseases (primary or secondary immune insufficiency, chronic kidney disease, nephritic syndrome, and immunosuppressive drug use) and those with endocrine disorders which may interfere with the optimal functioning of the pituitary-adrenal axis (diabetes mellitus, diabetes insipidus, hypo- or hyperthyroidism, precocious puberty, congenital adrenal hyperplasia, or pituitary insufficiency) were excluded. This study was approved by the İstanbul Medeniyet University Göztepe Training and Research Hospital, Clinical Research Ethics Committee (no: 2013/0011, date: 25.06.2013). Informed consent was received from the legal guardians of the children. This study was conducted in accordance with the principles of the Declaration of Helsinki.

The patients' demographic characteristics, clinical characteristics, type of JIA, arthritis localization, laboratory measurements, including complete blood count, C-reactive protein (CRP) level and rheumatoid factor (RF) levels, erythrocyte sedimentation rate (ESR), and number of joints with arthritis were recorded. The type of glucocorticoid, the treatment protocol, and the cumulative steroid dose were obtained from the patient files, in addition to the results of the low-dose (1 mcg) ACTH tests. The definition for AI was as follows: Having a serum cortisol level of <18 µg/dL 30 minutes after stimulation with ACTH.

The primary endpoint of this study was the difference in clinical characteristics, laboratory measurements and systemic corticosteroid dose in those children with AI and those without AI.

Statistical Analysis

The analyses were performed on the SPSS software, version 25.0 (SPSS Inc., Chicago, IL, USA). To check the normality of the distribution of continuous variables, the Shapiro-Wilk test was used. Continuous data obtained by descriptive analyses are given as mean ± standard deviation or median (1^{st} quartile - 3^{rd} quartile) according to the findings of normality analysis, and as frequency (absolute count and proportions) for categorical variables. Continuous variables which demonstrated normal distribution underwent testing with the independent samples t-test; whereas, those with non-normal distribution were analyzed with the Mann-Whitney U test. Categorical variable distributions were compared with chi-squared or Fisher's Exact tests. The significant risk factors independently associated with AI development were identified via multiple logistic regression analysis (forward conditional). P-values of <0.05 were accepted as being statistically significant.

Results

A total of 50 children [median age 12.35 (8.5-16.8) years] with JIA were analyzed. The comparison of those children with and without AI with regard to their clinical characteristics is given in Table I. The two groups were similar in terms of their ages, gender, body mass index and body surface area, Tanner stage, arthritis localization, joint scores, presence of morning stiffness, and the levels of leukocytes, CRP, and ESR at diagnosis.

Comparison of the laboratory tests is presented in Table II. Leukocyte count was significantly higher in those children with AI than in those without [9 (7.4-10.3)×10^3 vs. 7 (6-8)×10^3, p=0.008]. However, ESR was lower in those children with AI than in those without [13 (12-20) mm/hr vs. 21 (15-29) mm/hr, p=0.009]. Both baseline and stimulated cortisol levels were significantly lower in those children with AI than in those without AI (p<0.001). Finally, ACTH levels were also significantly lower in those children with AI than in those without [10.1 (5-29) vs. 17.9 (13.9-20.7), p=0.033].

The frequency of children receiving corticosteroids was higher among those with AI compared to those without AI [21 (84%) vs. 13 (52%), p=0.034]. However, the median cumulative steroid dose was significantly higher in those patients with AI compared to those without [2,500 (1,370-4,400) mg vs. 963 (650-2,500) mg, p=0.010]. The patients with AI were also grouped according to their daily dose. AI was detected in 60.9% (n=14) of those patients who used corticosteroids <10 mg/day, and 63.6% (n=7) of those patients who used corticosteroids >10 mg/day (p=0.052).

The duration of steroid use was similar between the two groups. The patients were categorized into two subgroups according to their duration of steroid use as those using for less than one month (short time) and those for more than one month (long time). The adrenal response was suppressed in 24% (n=2) of those patients using corticosteroids for less than one month and in 76% (n=23) for those patients using corticosteroids for longer than one month (p=0.009).

The relationship between steroid discontinuation time and AI was investigated in those patients who were not using corticosteroids at the time of their AI test. In 50% (n=2) of the patients with AI, steroid treatment had been discontinued less than one month previously [minimum (min): 14 days, maximum (max): 30 days], and in 50% (n=2) of them, more than one month previously (min: 31 days, max: 90 days). This result points out that in those patients whose steroid treatment was discontinued, AI may continue for more than one month after the treatment.

The amount and duration of corticosteroids used by our patients were divided into four groups as follows; 10 mg (low-dose) and above 10 mg (high-dose) for less than one month (short time) and more than one month (long time). According to these groups, among those patients using low-dose (<10 mg) corticosteroids, AI was not detected in any patient with a duration of less than one month of use; and AI was present in 46% (n=23) of those patients using both low and high doses for longer than one month. AI insufficiency was found in 40% (n=2) of patients using high doses (>10 mg) for a short time (<1 month), and in 83.3% (n=5) of patients using high doses (>10 mg) for a long time (>1 month) (p=0.01).

We performed multiple logistic regression analysis (forward conditional method) in order to determine any risk factors independently associated with AI (Table III). We found that the type of JIA and the cumulative steroid dose were significant risk factors. Patients with oligoarticular JIA had a 6.711-fold lower risk of AI than other types of JIA [odds ratio (OR): 0.149, 95% confidence interval (CI): 0.035-0.643, p=0.011] (Figure 1). Those patients with higher cumulative steroid dose (>1,000 mg) had a 7.5-fold higher risk of AI compared to those who had received lower dosages (OR: 7.5, 95% CI: 1,634-34,416, p=0.010) (Figure 2). Other variables included in the model, age (p=0.699), gender (p=0.286), family history (p=0.082), age at JIA onset (p=0.332), steroid use at stimulation testing (p=0.060) and the duration of steroid use (p=0.983) were found to be non-significant.

Discussion

This study aimed to investigate risk factors associated with AI in patients with JIA who had received systemic corticosteroids. Our findings show that those children developing AI during treatment with corticosteroids had received significantly higher cumulative corticosteroid doses compared to those children without AI. Moreover, having non-oligoarticular type JIA and cumulative corticosteroid doses were predictive for the development of AI during treatment with corticosteroids in children with JIA. Children with higher cumulative steroid doses (>1,000 mg) had a 7.5-fold higher risk of AI than those children with lower cumulative steroid doses (<1,000 mg).

JIA is the most common pediatric rheumatic disease in the world (12,13). The seven subtypes of JIA classified by the ILAR are oligoarticular, RF-positive polyarticular, RF-negative polyarticular, enthesitis-related arthritis, systemic onset, psoriatic arthritis, and undifferentiated arthritis (11). The prevalence of JIA is estimated to vary

Table I. Summary of patient- and JIA-related characteristics with regard to adrenal insufficiency

		Adrenal insufficiency		
	Total (n=50)	**No (n=25)**	**Yes (n=25)**	**p-value**
Age (years)	12.35 (8.5-16.8)	11.9 (8.5-16.5)	13.1 (9.5-16.8)	0.600
Gender				
Female	34 (68.00%)	19 (76.00%)	15 (60.00%)	0.363
Male	16 (32.00%)	6 (24.00%)	10 (40.00%)	
Height, m (SD)	-0.973±0.889	-0.896±0.75	-1,051±0.556	0.872
Weight, kg (SD)	-0.813±0.23	-0.624±0.25	-1,021±0.747	0.882
Body mass index, kg/m^2	18.62±3.55	18.90±3.59	18.33±3.56	0.575
Body surface are, m^2	1.27 (0.91-1.55)	1.36 (0.93-1.50)	1.23 (0.86-1.55)	0.992
Tanner stage				
Prepubertal	22 (44.00%)	12 (48.00%)	10 (40.00%)	0.776
Pubertal	28 (56.00%)	13 (52.00%)	15 (60.00%)	
Age at diagnosis (years)	9.56±4.45	9.02±4.52	10.10±4.41	0.397
Number of arthritis at diagnosis	2 (2-4)	2 (2-3)	2 (2-4)	0.630
Number of arthritis, last 6 months	2 (1-2)	2 (1-2)	2 (1-3)	0.584
Type of JIA				
Oligoarticular	31 (62.00%)	20 (80.00%)	11 (44.00%)	0.048
Polyarticular	9 (18.00%)	2 (8.00%)	7 (28.00%)	
Enthesitis-related	8 (16.00%)	3 (12.00%)	5 (20.00%)	
Systemic	2 (4.00%)	0 (0.00%)	2 (8.00%)	
WBC (x1000/mm^3) at diagnosis	8.9 (7-11.2)	9.7 (7.4-11.2)	8.8 (6.95-11.5)	0.676
ESR at diagnosis (mm/hr)	39 (25-57)	35 (22-65)	42 (30-52)	0.641
CRP at diagnosis (mg/dL)	1.85 (0.37-4.06)	1.90 (0.35-5.00)	1.80 (0.54-3.25)	0.961
RF positivity (units/mL)	2 (4.00%)	1 (4.00%)	1 (4.00%)	1.000
ANA positivity	9 (18.00%)	5 (20.00%)	4 (16.00%)	1.000
HLA-B27 positivity	4 (15.38%)	0 (0.00%)	4 (25.00%)	0.136
NSAID use	6 (14.29%)	3 (13.64%)	3 (15.00%)	1.000
Methotrexate use	17 (40.48%)	8 (36.36%)	9 (45.00%)	0.799
Sulfasalazine use	28 (66.67%)	13 (59.09%)	15 (75.00%)	0.444
Type of steroid				
Methylprednisolone	45 (90.00%)	24 (96.00%)	21 (84.00%)	0.349
Pulse steroid + methylprednisolone	5 (10.00%)	1 (4.00%)	4 (16.00%)	
Steroid use status				
Stopped	16 (32.00%)	12 (48.00%)	4 (16.00%)	0.034
Still using	34 (68.00%)	13 (52.00%)	21 (84.00%)	
Duration of steroid use, months	3 (2-6)	2.5 (1-6)	3 (2-6)	0.220
Cumulative steroid dose	1624 (750-3516)	963 (650-2500)	2500 (1370-4400)	0.010
Once every two days steroid use	18 (36.00%)	9 (36.00%)	9 (36.00%)	1.000
Remission	18 (42.86%)	10 (45.45%)	8 (40.00%)	0.964
Relapse	11 (61.11%)	6 (60.00%)	5 (62.50%)	1.000

Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables.
SD: Standard deviation, JIA: Juvenile idiopathic arthritis, WBC: White blood cells, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, RF: Rheumatoid factor, ANA: Anti-nucleus antibody, HLA: Human leukocyte antigen, NSAID: Non-steroid anti-inflammatory drugs

Table II. Summary of laboratory measurements with regard to adrenal insufficiency

		Adrenal insufficiency		
	Total (n=50)	**No (n=25)**	**Yes (n=25)**	**p-value**
WBC (x1000/mm^3)	7.75 (6.6-9.6)	7 (6-8)	9 (7.4-10.3)	0.008
ESR (mm/hr)	16.5 (13-27)	21 (15-29)	13 (12-20)	0.009
CRP (mg/dL)	0.33 (0.33-0.80)	0.33 (0.30-0.51)	0.33 (0.33-0.88)	0.857
Insulin (µIU/mL)	8.51 (5.95-11.60)	8.24 (6.67-10.44)	8.78 (5.94-13.64)	0.637
Free T4 (ng/dL)	0.89 (0.78-1.03)	0.82 (0.77-0.96)	0.94 (0.86-1.17)	0.030
TSH (µIU/mL)	1.85 (1.36-3.06)	1.88 (1.38-3.56)	1.74 (1.32-2.79)	0.750
Fasting blood glucose (mg/dL)	85 (80-90)	86 (79-91)	85 (80-90)	0.826
HOMA-IR (mIU/L)	1.73 (1.19-2.51)	1.68 (1.38-2.38)	2.03 (1.13-2.86)	0.733
Triglyceride (mmol/L)	68.65±24.31	65.65±15.92	71.65±30.60	0.410
Total cholesterol (mg/dL)	161 (136-191)	159 (136-188)	180 (136-208)	0.169
LDL (mg/dL)	93.76±26.51	89.22±24.75	98.30±27.96	0.250
HDL (mg/dL)	60.52±15.84	56.74±12.88	64.30±17.83	0.107
Baseline cortisol (mcg/dL)	8.08 (1.41-11.91)	11.60 (7.45-12.72)	1.41 (0.52-10.10)	<0.001
Stimulated cortisol (mcg/dL)	17.87 (10.03-20.73)	20.73 (19.60-21.43)	10.03 (5.31-15.30)	<0.001
Baseline DHEA-S (µmol/L)	32.9 (6.6-89.4)	42.1 (6.9-158.4)	19.1 (2.8-51.0)	0.133
Stimulated DHEA-S (µmol/L)	36.25 (6-96.2)	42.9 (6.6-159.3)	20.1 (2.7-57)	0.154
ACTH (pg/mL)	14.65 (7.37-21.3)	17.9 (13.9-20.7)	10.1 (5-29)	0.033

Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables.
WBC: White blood cells, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, TSH: Thyroid stimulating hormone, HOMA-IR: Homeostatic model assessment for insulin resistance, LDL: Low dansity lipoprotein, HDL: High dansity lipoprotein, DHEA-S: Dehydroepiandrosterone sulfate, ACTH: Adrenocorticotropic hormon

Table III. Significant risk factors of adrenal insufficiency, multiple logistic regression analysis

	β coefficient	**Standard Error**	**p-value**	**Exp (β)**	**95% CI for Exp (β)**	
Type of JIA (oligoarticular)	-1.902	0.745	0.011	0.149	0.035	0.643
Cumulative steroid dose (>1000 mg)	2.015	0.777	0.010	7.500	1.634	34.416
Constant	-0.161	0.697	0.818	0.852		
Dependent variable: Adrenal insufficiency; nagelkerke R^2=0.351; correct prediction=72.00%						
JIA: Juvenile idiopathic arthritis, CI: Confidence interval						

between 16 and 150 per 100,000 individuals. The clinical features of JIA differ greatly according to the type of disease. Greater severity of arthritis at onset, symmetrical disease, early wrist or hip involvement, the presence of RF, persistent active disease, and early radiographic changes are indicative of poor prognosis in children with JIA, and therefore, are often relevant to treatment decisions (14). There are various studies which have examined risk factors for steroid-induced AI (15), but information is lacking where specific diseases and pediatric patients are concerned (16).

Understanding the aforementioned basis of therapy is crucial for the management of JIA, as it requires a multimodal approach including pharmacological interventions, physical and occupational therapy, and psychosocial support (17,18). Additionally, the potential side effects of ever-changing therapeutic approaches necessitate the constant evaluation of factors associated with these side effects. NSAIDs and the intra-articular injection of triamcinolone hexacetonide are the first-line treatment options frequently used in those children with JIA (19,20). However, in those children whose disease is poorly controlled by these approaches, the selective use of systemic corticosteroids may be considered

despite their potentially serious side effects, such as growth failure, obesity, hypertension, hyperglycemia, osteoporosis and/or muscle weakness. Even intra-articular glucocorticoid administration has been occasionally associated with iatrogenic AI, and the systemic use of glucocorticoids frequently leads to a suppression of the hypothalamic-pituitary-adrenal axis (21-23), while adverse effects on growth and bone health have also been reported (24).

Data concerning the predictors of secondary AI in JIA patients receiving systemic corticosteroids is lacking. Our findings show that AI was more prevalent among those children who were still on systemic corticosteroids and those with a higher cumulative dose of systemic corticosteroids. Multiple logistic regression analysis revealed that being diagnosed with non-oligoarticular type JIA and having received a cumulative steroid dose of >1,000 mg were the only two factors predictive for AI. Previous studies on patients with JIA have shown that low-dose glucocorticoid treatment, even when applied for extended periods, did not increase the risk of AI (25), which supports our results. From this point of view, it is clear that the use of systemic corticosteroids should be reserved only for more aggressive types of JIA and in JIA types with non-favorable long-term prognosis. Additionally, our data indicates that local administration should be preferred to systemic administration if possible. Although this approach has the potential to be satisfactory in some patients, intra-articular corticosteroids cause partial suppression of cortisol production (26) and some studies have reported a considerable rate of transient or long-lasting AI development in JIA cases receiving intra-articular corticosteroid injections. In those studies, AI likelihood was associated with the child's age (27) and the injection dosage (27,28). Earlier studies also suggested a relationship between cushingoid appearance and the number of joints to which steroid injections had been performed (29). These findings infer support to our conclusion regarding cumulative dosage, and it is evident that more studies focusing on this topic are required, especially considering certain case reports

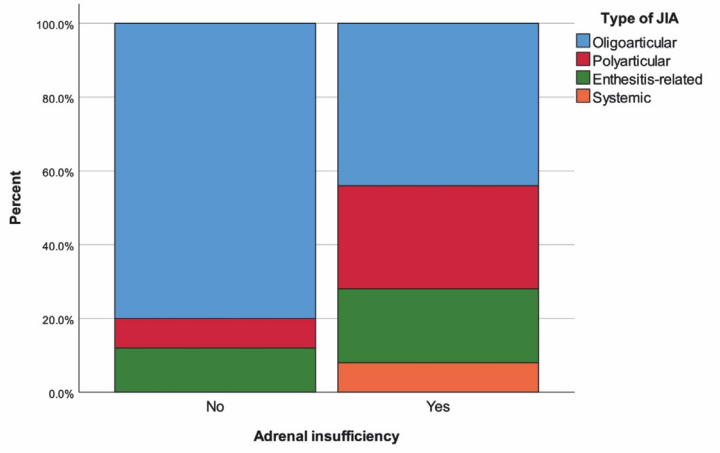

Figure 1. Type of JIA with regard to adrenal insufficiency
JIA: Juvenile idiopathic arthritis

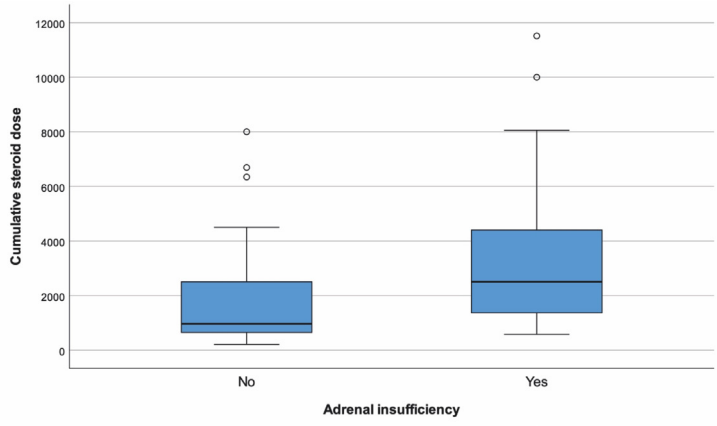

Figure 2. Cumulative steroid dose with regard to adrenal insufficiency

which have demonstrated the development of Cushing's syndrome in patients with JIA who had received intra-articular corticosteroid treatment (21,30).

Clinicians should be aware that they should seek methods allowing for the limitation of the cumulative dose of systemic corticosteroids administered, particularly below 1,000 mg. With this in mind, our findings indicate for the first time that a high cumulative dosage of corticosteroids is predictive for the development of AI in those patients who receive systemic corticosteroids for JIA management.

Study Limitations

There are some limitations to be mentioned. First, this was a retrospective data analysis. Second, our sample size was relatively small. Further prospective data with a larger sample size will be necessary to support the results of this study and to clarify the factors associated with AI in JIA patients receiving systemic corticosteroids.

Conclusion

In conclusion, AI is a serious side effect of systemic corticosteroids in children with JIA. Our findings show that presence of non-oligoarticular JIA and a high cumulative corticosteroid dose are predictive for the development of AI in this patient subset. We believe that systemic corticosteroids should be reserved only for more aggressive types of JIA and that, in patients requiring corticosteroids, the cumulative dose should be limited to 1,000 mg in order to prevent the development of AI.

Ethics

Ethics Committee Approval: This study was approved by the İstanbul Medeniyet University Göztepe Training and Research Hospital, Clinical Research Ethics Committee (no: 2013/0011, date: 25.06.2013).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.Z.E., Concept: G.Z.E., M.E., M.Y., Design: G.Z.E., M.E., M.Y., Data Collection or Processing: G.Z.E., M.E., Analysis or Interpretation: G.Z.E., Literature Search: G.Z.E., Writing: G.Z.E.

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Original Article

Comparative Evaluation of Clinical, Spiro/ Oscillometric and Tomographic Parameters as a Global Assessment of Children with Cystic Fibrosis

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ABSTRACT

Aim: The aim of our study was to compare clinical severity scores and classic spirometry with impulse oscillometry (IOS) results and thoracic high resolution computed tomography (HRCT) scores in children with cystic fibrosis (CF) in order to determine the utility of the latter approach in patient follow-up.

Materials and Methods: CF patients over 6 years of age were included. Shwachman-Kulczycki score, underclassical spirometry and IOS were performed when not in acute exacerbation. Thoracic HRCT images obtained within the previous 6 months were evaluated using the Bhalla scoring system.

Results: The mean age of the children studied (n=30) was 12.1±4.2 years and 40% were female. *Pseudomonas aeruginosa (P. aeroginosa)* was isolated from sputum cultures of 40% of the patients. Patients with forced expiratory volume in one second (FEV1) below 80% exhibited significantly higher (resistance) R5, R10 values and significantly lower (reactance) X5 values on IOS (p=0.03, 0.027, 0.006, respectively). Patients with *P. aeruginosa* had significantly lower FEV1, forced vital capacity, and forced expiratory flow (25-75) values in classic spirometry when compared with patients without *P. aeruginosa* (p=0.002, p=0.002, and p=0.005, respectively). *P. aeruginosa*-positive patients showed significantly higher R5 and lower X5 values (p=0.047, 0.046, respectively). Bhalla scoring, bronchiectasis weight, peribronchial thickening, mucous plaques, saccularization, bronchial division, mosaic pattern parameters in groups with *P. aeroginosa* growth and/or FEV1 <80%; was found to be significantly more serious than the non-reproductive group (p<0.005, respectively). Again, in the group with *P. aeroginosa* growth, Shwachman-Kulczycki score was found to be significantly lower (p=0.001). No significant correlation was found between thoracic score data such as bronchiectasis weight and mosaic pattern presence and IOS values. In addition, in the group with high clinical score of Shwachman Kulczycki, resistance values such as R5 R10 R15 which are IOS parameters, and FEV1 were found above 80% (p=0.016, p=0.037, p=0.042, 0.004, respectively).

Conclusion: IOS and tomographic scoring can be used safely in early detection of impairment in lung function. Further studies are needed to evaluate the utility of IOS in the clinical monitoring of children with CF who are not compliant with spirometry maneuvers.

Keywords: Bhalla, cystic fibrosis, spirometry, impulse oscillometry, thoracic HRCT

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Introduction

Because pulmonary complications are responsible for the majority of mortality and morbidity in children with cystic fibrosis (CF), monitoring pulmonary function and detecting declines early are of critical importance (1,2). However, there is still no reliable method or combination of methods for assessing respiratory function. Disease severity scores are often related to the severity of airway disease (3). Pulmonary function testing, sputum culture, lung imaging methods, and scoring systems can be used to assess pulmonary involvement. In the stages when clinical findings can be detected in children, significant deterioration has occurred in pulmonary function tests (2,4). A major reason for this is that the spirometric methods routinely used to measure pulmonary functions require maneuvers that children cannot perform, especially at very young ages (5). Classic spirometry is used to demonstrate pulmonary functions in CF patients, and forced expiratory volume in one second (FEV1) has been associated with hospitalization and risk of death (5). However, due to problems with patient compliance, this method cannot be used in early childhood, when initial and substantial loss of lung function occurs. Reliable tests are needed to monitor pulmonary functions in young children who cannot undergo spirometry. The forced oscillation technique is a method of pulmonary function testing that is easy to use, does not require patient cooperation, and assesses airway resistance and reactance (6). Demonstration of its utility in CF will provide important data in the follow-up of lung involvement. In addition to pulmonary function tests, clinical scoring systems including data such as general activity, physical examination findings, infectious colonization, nutrition, and weight gain are used when following CF patients. A study using the Shwachman-Kulczycki score determined that decreasing score was significantly correlated with decline in respiratory function, lower body mass index (BMI), and infectious colonization (3). Similarly, higher scores were associated with better pulmonary function and quality of life in a study in which disease progression was assessed using spirometry, BMI, Fuchs criteria (exacerbation index), and the CF respiratory symptom diary-chronic respiratory infection symptom score (3). Radiological scoring systems are also used to assess pulmonary involvement in patients with CF. In many studies, patients with low spirometry FEV1 values showed deterioration of thoracic computed tomography (CT) scans showing pulmonary involvement, as well as lower radiological scores in patients with chronic infectious colitis (7,8).

The aim of this study is to show the effectiveness of impulse oscillometry (IOS) in respiratory functions by comparing pulmonary involvement, pulmonary function tests such as spirometry, IOS and Thorax high resolution computed tomography (HRCT) scores in patients followed up with the diagnosis of CF.

Materials and Methods

Study Population

The study included 30 consecutive patients over 6 years of age who were being followed in the Pediatric Allergy and Pulmonary Diseases Units of Manisa Celal Bayar University and Izmir Katip Celebi University with a diagnosis of CF and agreed to participate in study. CF diagnosis was based on clinical findings with two positive sweat tests and positive CF mutation analysis.

Study Design and Ethics Approval

This cross-sectional study was approved by the Manisa Celal Bayar University Clinical Research Ethics Committee (decision number: 20478486-202 dated 7 May, 2014).

Data Collection

Age, gender, weight and height percentiles, age at CF diagnosis, sweat test and CF mutation analysis results, and bacterial isolation from throat or sputum culture were recorded for all participants. More than one *P. aeroginosa* growth or chronic colonization in sputum culture was considered positive for the presence of *P. aeruginosa*. Thoracic HRCT images taken within the last 6 months were assessed using the Bhalla scoring system (9). IOS and spirometry values were recorded when patients were enrolled to the study. Pulmonary function tests were performed outside periods of acute exacerbations. Patients with congenital or secondary heart disease were excluded from the study.

Evaluation of Clinical Severity

For clinical evaluation of the patients we used the Shwachman-Kulczycki score, which includes general activity, physical examination, nutrition, and radiological findings (10). The criteria used in this scoring system for these four domains are: decrease in endurance, exercise symptoms, and presence of orthopnea for general activity; weight, muscle mass, abdominal distension, abnormal stool, and rectal prolapse for nutrition; digital clubbing, respiration rate, and hyperinflation for physical examination; and atelectasis, hyperinflation, and bronchiectasis as radiographic signs. According to the patient's findings, each domain is scored as 5, 10, 15, 20, or 25. The domain scores are summed to

obtain a total clinical condition score, which is categorized in one of 5 grades as excellent (86-100), good (71-85), average (56-70), poor (41-55), and severe (<40).

Assessment of Pulmonary Function

Classic Spirometry: Spirometry was performed with a Jager MS-IOS (care fusion/Germany) device. Forced vital capacity (FVC) and FEV1, [peak expiratory flow, forced expiratory flow (FEF) 25-75] were measured during respiratory maneuvers. After performing numerous measurements, the result of the trial in which the patient was most cooperative and achieved the best result was chosen for analysis.

Impulse Oscillometry Measurement: IOS was applied with the Jager MS-IOS (master screen IOS, care fusion/Germany) device. The measurements were taken with a device stored in appropriate humidity and temperature and calibrated daily. Prior to measurements, the children were informed about the procedure and trials were done to familiarize them. The patients were asked to sit in a comfortable position, hold their head erect, and breathe normally while wearing a mouth mask. In addition, a technician supported their cheeks and mouth in order to minimize vibrations of the upper airway. The frequencies of the pressure oscillations delivered ranged between 5 to 30 and 30 s measurements were obtained regularly. After performing the maneuver at least three times, the best measurement was recorded. Airway resistance (R, resistance), elastic capacity (X, reactance), and pulmonary impedance (Z) values were recorded at 5, 10, and 15 Hz. Results with values of 0.6 at 5 Hz and 0.8 at 10 Hz in the "validity" section were considered valid (11). Spirometry and IOS results were compared for the evaluation of respiratory functions.

Thoracic HRCT Scoring

CT scans were obtained using a Toshiba (Aquilion) 128 multi-slice CT instrument with parameters of 120 mKV and 180 mA and no contrast with the patient lying in supine position after being instructed to hold their breath for 5 seconds. On average, series of 1 mm thick cross-sectional images were obtained at 10 mm intervals from the lung apex to the base.

The patients' thoracic HRCT images were scored by a pediatric radiologist blinded to their clinical condition and pulmonary function test results. Ten features were identified on thoracic tomography: pulmonary bronchiectasis, peribronchial thickening, mucus plugs, abscess, bulla, emphysema, gas trapping or hyperinflation, mosaic perfusion or opacities, collapse or consolidation, and presence of intralobular or interlobular septal thickening. The modified Bhalla scoring system was used to evaluate these findings (9). Each criterion in the scoring system received 0 points for no pathology and 1 to 3 points if pathology was detected.

Statistical Analysis

Statistical analysis of the acquired data was done using statistical package for the social sciences (SPSS) 18.0 (SPSS Inc., Chicago, IL, USA) package software. Continuous variables were expressed as mean ± standard deviation (minimum-maximum) and categorical variables were expressed as number and percentage (%). Chi-square test was used for comparison of qualitative variables between groups, Student's t-test was used for comparison of data with normal distribution, and Mann-Whitney U tests were used for comparison of data with non-normal distribution. The correlation of the parameters was evaluated with the Pearson correlation test. P-values less than 0.05 were accepted as statistically significant.

Results

Demographic Characteristics

The mean age of the children studied (n=30) was 12.1±4.2 years and 40% were female. The age at CF diagnosis was 3.7±3.4 years. The most common CF mutation among the patients was delF508 (61%), and no mutation could be identified in 5 patients (23%) (Table I).

Clinical Findings

Clinical condition was excellent (86-100) in 40% of the patients, good (71-85) in 30%, average (56-70) in 13.3%, and poor (41-55) in 16.7%. No patients were in severe (<40) clinical condition. *P. aeruginosa* was detected in the sputum cultures of 40% of the patients (Table I). Shwachman scores were lower in the group of patients from whom *P. aeruginosa* was isolated (p=0.001). In the group with high Shwachman-Kulczycki scoring, the resistance value such as R5 R10 R15, which are IOS parameters, was found to be low and X5 reactance value was significantly higher (p=0.016, p=0.037, p=0.042, p=0.047, respectively). In addition, in the group with high Shwachman-Kulczycki score (excellent and good group), FEV1 was found above 80% (p=0.004) (chi-square test).

Pulmonary Function Test Findings

Classic Spirometry Results: FEV1, FVC, FEF25-75 values obtained in spirometry were significantly lower in

patients with *P. aeruginosa* than those without (p=0.002, p=0.002, and p=0.005, respectively) (Table II).

Impulse Oscillometry Results: The *P. aeruginosa*-positive patients showed significantly higher R5 (resistance) and lower X5 (reactance) values (p=0.047 and 0.046, respectively) (Table II).

Patients with FEV1 below 80% exhibited significantly higher R5 and R10 (resistance) values and significantly lower X5 reactance values (p=0.03, 0.027, and 0.006, respectively) (Table III) (Figures 1 and 2).

Radiologic Findings: Bronchiectasis was present in 20 patients (66.6%), peribronchial thickening in 20 (66.6%),

Table I. Demographic and clinical characteristics

	Patient group (n=30)
Age*	12.1±4.2
Gender** Male Female	 18 (60) 12 (40)
CF diagnosis*	3.7±3.4
Mutation** Del F508 (n/%) Other (n/%) Undetectable (n/%)	 18 (61) 5 (16) 7 (23)
*P. aeroginosa*** Positive	 12 (40)
Clinical scores** Excellent Good Mild Average Severe	 12 (40) 9 (30) 4 (13.3) 5 (16.7) 0 (0)

CF: Cystic fibrosis, ***P. aeroginos: Pseudomonas aeruginosa***
*Mean ± standard deviation, **Number (%)

Table II. Comparison of FEV1 and impuls ossilometry values with *Pseudomonas aseroginosa* positive/negative patients

	***P. aeroginosa* (-)**	***P. aeroginosa* (+)**	**p-value****
FEV1* (%)	**102 (32)**	**52.6 (50.68)**	**0.002**
FVC* (%)	**103.0 (35.5)**	**70.5 (51.0)**	**0.002**
PEF * (%)	74 (20)	60.4 (30.28)	0.192
FEF25/75* (%)	**90.5 (36.4)**	**26.5 (51.6)**	**0.005**
R5 %*	**96.1 (42.60)**	**149.5 (76.0)**	**0.047**
R5* [kPa(L/s)]	**0,54 (0.23)**	**0.79 (0.23)**	**0.037**
R10* %	101.0 (43.90)	118.35 (51.50)	0.150
R10* [kPa(L/s)]	0.53 (0.28)	0.51 (0.17)	0.456
R15 %*	93.50 (48.55)	113.70 (29.70)	0.275
R15* [kPa(L/s)]	0.48 (0.20)	0.42 (0.18)	0.347
X5 %*	**37.3 (138.85)**	**172.05 (183.53)**	**0.046**
X5* [kPa(L/s)]	**-0.089 (0.27)**	**-0.28 (0.42)**	**0.05**
X10 %*	134.4 (135.5)	308.30 (286.50)	0.194
X10* [kPa(L/s)]	-0.11 (0.17)	-0.20 (0.16)	0.152
X15 %*	50.6 (93.55)	103.0 (104.95)	0.458
X15* [kPa(L/s)]	-0.078 (0.15)	-0.16 (0.13)	0.164
Z5 %*	**105 (55.2)**	**132 (35.67)**	**0.047**

P. aeroginosa: Pseudomonas aeruginosa, FEV1: Forced expiratory volume in one second, FVC: Forced vital capacity, PEF: Peak expiratory flow
*Median (interquartile range), **Mann-Whitney U test

mucus plaques in 15 (50%), secularization in 6 (20%), bronchial deviation in 20 (66.6%), mosaic pattern in 19 (63%), and collapse in 8 patients (26.6%).

Similarly, patients with FEV1 below 80% showed significantly more severe bronchiectasis, peribronchial thickening, mucus plaques, mosaic perfusion and bronchial deviation compared to patients with FEV1 over 80% (p=0.006, 0.000, 0.012, 0.000, 0.003, respectively) (Table IV) (r=-0.52, -0.61, -0.66, -0.55, -0.30). No significant correlation was found between thoracic score data such as bronchiectasis weight and mosaic pattern presence and IOS values (p>0.05).

The *P. aeruginosa*-positive group also had significantly more severe bronchiectasis, peribronchial thickening, mucus plaques, secularization, bronchial division, and mosaic pattern when compared to patients who were negative for *P. aeruginosa* (p=0.006, 0.00, 0.012, 0.002, 0.003, 0.00, respectively (Table V).

Table III. Comparison of FEV1 values and impuls ossilometry values of patients

	FEV <80% (n=12)	**FEV >80% (n=18)**	**p-value****
R5%*	**160.0 (88.7)**	**98.3 (46.5)**	**0.03**
R5* [kPa(L/s)]	**0.75 (0.37)**	**0.56 (0.34)**	**0.045**
R10%*	**120.1 (53.0)**	**104.5 (34.7)**	**0.027**
R10* [kPa(L/s)]	0.488 (0.09)	0.57 (0.27)	0.388
R15%*	114.0 (49.05)	93.7 (47.43)	0.051
R15* [kPa(L/s)]	0.42 (0.06)	0.49 (0.25)	0.388
X5%*	**176.1 (181.6)**	**45.45 (119.57)**	**0.006**
X5* [kPa(L/s)]	**-0.35 (0.31)**	**0.06 (0.33)**	**0.000**
X10%*	376.6 (512.5)	147.3 (99.8)	0.208
X10* [kPa(L/s)]	-0.23 (0.21)	-0.12 (0.16)	0.09
X15%*	105.0 (125.0)	72.8 (108.1)	0.345
X15* [kPa(L/s)]	-0.189 (0.17)	-0.088 (0.13)	0.214
Z5%*	**140 (47.28)**	**102 (55.53)**	**0.004**

FEV: Forced expiratory volume
*Median (interquartile range), **Mann-Whitney U test

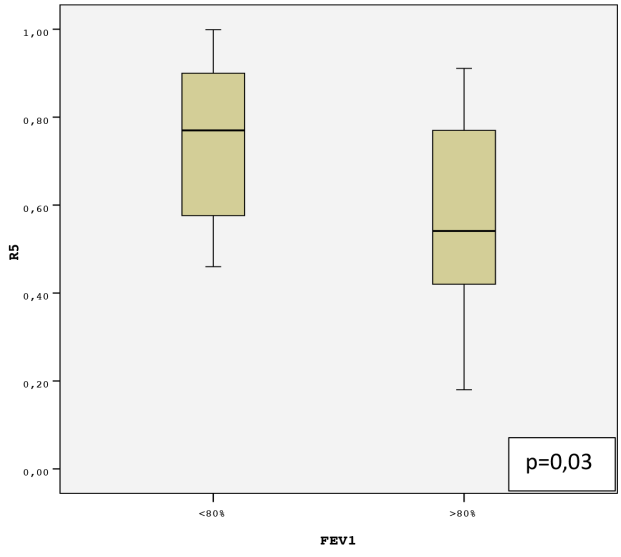

Figure 1. Comparison of FEV1 and R5 values
FEV1: Forced expiratory volume in one second

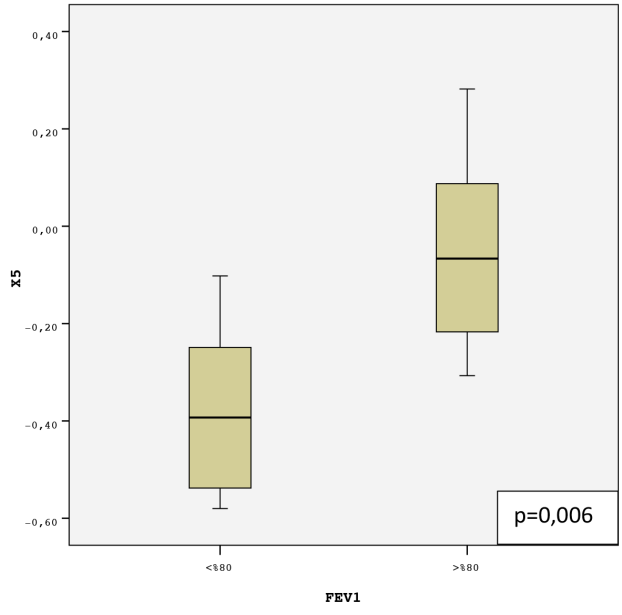

Figure 2. Comparison of FEV1 and X5 values
FEV1: Forced expiratory volume in one second

Table IV. FEV values and thorax HRCT findings in patients with cystic fibrosis

	FEV <80%* (n=12)	**FEV >80%* (n=18)**	**p-value****
Bronchiectasis	**1.90 (1.10)**	**0.75 (0.85)**	**0.006**
Peribronchial thickening	**1.90 (0.99)**	**0.75 (0.68)**	**0.002**
Mucus plaques	**2.0 (0.92)**	**0.5 (0.89)**	**0.000**
Mosaic perfusion	**2.2 (0.91)**	**0.87 (1.02)**	**0.003**
Bronchial deviation	2.4 (1.07)	1.5 (1.46)	0.106
Emphysema	0.40 (0.84)	0.00 (0.00)	0.067
Collapse-consolidation	0.40 (0.69)	0.25 (0.44)	0.509
Bhalla scor	**15.50 (6.5)**	**7.0 (5.55)**	**0.001**

FEV: Forced expiratory volume, HRCT: High resolution computed tomography
*Median (interquartile range) **Mann-Whitney U test

Table V. Thorax HRCT findings and presence of pseudomonas in patients with cystic fibrosis

	***P. aeroginosa* (-)* (n=18)**	***P. aeroginosa* (+)* (n=12)**	**p-value****
Bronchiectasis	**0.70 (0.98)**	**1.75 (0.86)**	**0.006**
Peribronchial thickening	**0.64 (0.70)**	**1.8 (0.83)**	**0.000**
Mucus plaques	**0.52 (1.06)**	**1.58 (0.99)**	**0.012**
Mosaic perfusion	**0.70 (0.98)**	**2.3 (0.49)**	**0.000**
Bronchial deviation	**1.23 (1.43)**	**2.6 (0.6)**	**0.003**
Emphysema	0.11 (0.48)	0.16 (0.57)	0.806
Collapse-consolidation	0.23 (0.43)	0.41 (0.66)	0.384
Bhalla scor	**2.5 (12.50)**	**13.50 (6.50)**	**0.003**

P. aeroginos: Pseudomonas aeruginosa
*Median (interquartile range) **Mann-Whitney U test

Discussion

In the present study, we evaluated the pulmonary functions of 30 CF patients over 6 years old using classic spirometry and IOS and compared them based on the detection of *P. aeruginosa* in sputum cultures and thoracic HRCT scores. Patients with FEV1 <80% in spirometry were found to have significantly higher R5 and R10 values and lower X5 reactance values in IOS. In addition, patients with chronic lung sequelae and *P. aeruginosa* colonization exhibited low FEV1 values and a proportionate increase in resistance and decrease in reactance. However, no significant correlation was found between the findings of chronic lung changes and IOS values.

CF is a chronic disease with progressive lung damage and decline in pulmonary function (1). Respiratory system involvement begins from infancy and lung injury occurs due to chronic inflammation and infection as the disease progresses. Chronic structural changes in the peripheral and central airways also occur in early CF, leading to decline in pulmonary function (11,12). Children who are not diagnosed at an early age, do not receive adequate treatment, and have progressive CF have lower respiratory function and worse quality of life due to early airway injury. Providing airway clearance therapy, practicing microbial surveillance and strategic antibiotic use in pulmonary infections, and properly monitoring pulmonary functions from the early stages are crucial for a better prognosis (13-15). Therefore, sensitive, minimally invasive tests are needed to demonstrate early pulmonary involvement and function in young children. Data regarding the follow-up of lung function in young children is limited due to the difficulty of performing pulmonary function tests in this age group. In some studies, pulmonary function in infant and preschool-aged CF patients was assessed with rapid expiratory flow and volumetric measurements using thoracoabdominal compression techniques. This method is difficult to apply, but has been used to show that airway resistance

increases between infancy and preschool age (16,17). Other studies have also evaluated pulmonary functions with gas techniques (multibreath washout), and although important data have been obtained regarding disease progression, they are difficult to apply and thus have been adopted in routine practice (15). After reaching school age, compliance with classic spirometry and regular FEV1 measurements enables monitoring of respiratory functions in these patients (18). However, the early onset of disease and patient non-compliance limit the use of this method. IOS is a pulmonary function test method that requires minimal patient cooperation, can be measured during normal breathing, is easy to apply, and evaluates airway resistance and elastic capacity. There are few studies regarding the use of IOS in patients with CF. In a study by Gangell et al. (19) including 56 CF patients, IOS resistance values were higher and reactance values were lower in CF patients compared to controls. In a study using spirometry and IOS to evaluate 49 CF patients during periods of acute exacerbation and remission, the patients showed higher R5,10,15 resistance values and lower X5,10,15 reactance values compared to the control group, and acute exacerbation was also associated with higher resistance values and lower reactance values within the patient group. The same study also determined that changes in IOS values were consistent with spirometry values (20). In another study comparing the spirometry and IOS values of CF patients, R5 resistance value was negatively correlated with FEV1 value, while no significant correlations with reactance value could be shown, and the authors stated that IOS could provide an alternative method to spirometry (21). Conversely, in another study evaluating IOS in the assessment of pulmonary function in CF patients, it was observed that although IOS parameters correlated with spirometry values, the results were not consistent with age-standardized parameters such as FEV1, and therefore the authors concluded that the technique was not reliable enough (22). A comparison of spirometry and IOS results in 34 CF patients during acute pulmonary exacerbation and remission demonstrated that despite a correlation between IOS and spirometry values, there were no significant differences in IOS measurements between acute exacerbation and remission periods (23).

In our study, a significant relationship was found between FEV1 value and R5 and X5 values, which show airway resistance and flexibility in small airways, and this relationship was observed to continue significantly in patients with FEV1 <80%. Although there are no safe values for age and gender in the grading of pulmonary insufficiency for IOS yet, it will be useful to follow these values in the long-term clinical follow-up of CF patients, especially those who are at an early age and cannot perform classical spirometry.

The thick secretions and inflammatory process of CF create a suitable environment for chronic infection, and thus play an important role in the mortality and morbidity of the disease. *P. aeroginosa, Staphylococcus aureus (S. aureus), Haemophilus influenza (H. influenza), and Stenotrophomonas maltophilia* are most commonly implicated in the pathogenesis of permanent parenchymal damage. In many studies, the use of broad-spectrum, and especially anti-pseudomonal antibiotics has been associated with improved respiratory function and increased life spans in CF patients (24). While infection and inflammatory processes cannot be clearly distinguished in these patients, reduced lung function and decreased FEV1 has been observed in those with pseudomonal infection or colonization (14). In a retrospective study of 770 CF patients, those with *P. aeruginosa* and methicillin-resistant *S. aureus* colonization showed reduced lung function and higher mortality and morbidity (25). In another study, the detection of proinflammatory pathogens (*P. aeruginosa*, *H. influenzae, Aspergillus* spp., *Streptococcus pneumoniae*) in bronchoalveolar lavage from young CF patients was clinically associated with deterioration of pulmonary function (26). In the present study, spirometry values (FEV1, FVC, FEF25-75) were lower in patients with *P. aeruginosa*-positive sputum cultures, while R5 resistance values were significantly higher and X5 reactance values were lower in IOS. Therefore, in CF patients with infectious colonization for whom FEV1 is being used to monitor pulmonary function, IOS can also be safely used to demonstrate pulmonary functions such as airway resistance and elastic capacity.

Several prospective studies have shown that pulmonary parenchymal changes, including bronchiectasis, may occur in CF during infancy and may be more common in patients with infection and inflammation during the first year of life, and that bronchiectasis was associated with increased morbidity and reduced pulmonary function (15,27). Because bronchiectasis and other accompanying chronic sequelae are sensitive indicators of disease progression, CT is used as a sensitive method for the early detection of pulmonary changes (27). In addition, many studies have reported that HRCT enabled more sensitive and earlier detection of pulmonary progression compared to spirometry. A positive correlation was also observed between bronchiectasis severity and infectious colonization (28,29). A study in which 31 CF patients were prospectively monitored by spirometry

and assessed by repeated HRCT scoring over a period of 4 years showed that HRCT progression preceded the deterioration of spirometry results (29). Similarly, another study evaluating 87 CF patients showed that thoracic HRCT findings were more sensitive than pulmonary function tests in detecting early and small changes in the lungs (30). In the CF patients in our study, we found a significant correlation between the degree of decline in thoracic HRCT scores and FEV1 values, and these patients also exhibited an increase in R5 and R10 resistance values and decrease in X5 reactance values. However, no significant correlation was found between the weight of chronic changes such as bronchiectasis weight or mosaic pattern presence and IOS parameters. For this situation, it is thought that more studies with more cases are needed.

Many scoring methods were used to evaluate the clinical severity of the disease. The Shwachman-Kulczycki score is a useful tool to monitor the severity of CF, which also adequately reflects chest radiography changes, especially in patients with marked lung dysfunction (31,32). Although it does not take into account the pulmonary function test, it is still the most commonly used score. In our study, higher spirometry values were found in patients with excellent-good score, and it was also found to be associated with lower resistance (R5, R10, R15) and higher reactance (X5) values.

Study Limitations

The small number and diversity of cases in our study is an important limitation. Despite this, the study demonstrated the use of IOS as a reliable tool for disease monitoring in children with CF.

Conclusion

In conclusion, deterioration of pulmonary function and worsening of thoracic HRCT scores can occur from infancy in CF patients; therefore, monitoring pulmonary function from an early age is crucial in these patients. The combined use of clinical, spirometric, and HRCT radiological methods as a global assessment of pulmonary function may yield more realistic results. In addition, IOS may be used in the follow-up of pulmonary disease in CF patients to detect decline in respiratory functions from early ages, and even before the appearance of significant clinical findings. However, there is a need for more prospective studies which involve the comparative evaluations described herein to standardize IOS thresholds for young children.

Ethics

Ethics Committee Approval: This cross-sectional study was approved by the Celal Bayar University Clinical Research Ethics Committee (decision number: 20478486- 202 and dated 7 May, 2014).

Informed Consent: Informed consent was taken from the participants.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Data Collection or Processing: A.K., E.E.Ö., Y.Ş., Analysis or Interpretation: E.T.K., Ö.Y., A.K., H.H.A., Writing: E.T.K., Ö.Y., H.Y.

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

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Original Article

Effects of White Noise and Facilitated Tucking During Heel Stick Sampling on the Pain Response of Healthy Term Newborns: A Randomized Controlled Study

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ABSTRACT

Aim: Painful procedures in the newborn begin with injections. Controlling painful practices in the newborn is of great importance. Nurses should be familiar with evidence-based non-pharmacological methods to reduce pain. This study was performed to compare the effect of white noise, facilitated tucking, and their concerted application during heel-stick sampling on pain in term babies.

Materials and Methods: A randomized controlled trial was conducted. The study was conducted on 90 newborns. Using stratification and the blocking method, 30 newborns were included in the white noise group (Group 1), 30 in the facilitated tucking group (Group 2), and 30 in the white noise + facilitated tucking group (Group 3). Pain scores of the newborns in all groups before, during, and after the procedure were evaluated by two nurses independent of each other using the neonatal infant pain scale (NIPS).

Results: When the NIPS scores of the neonates during the heel-stick sampling procedure were compared, a significant difference was detected between the groups ($p<0.001$).

Conclusion: The pain score of the group that was made to listen to white noise and had been placed in the facilitated tucking position during the application was significantly lower than in the other two groups.

Keywords: Facilitated tucking, newborn, pain, white noise

Introduction

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with or resembling actual or potential tissue damage" (1). Pain begins to be felt in intrauterine life when the fetus is in the 20-24th gestational week. It has in fact been determined that the fetus can respond to pain from the first week of life (2). Metabolic, hormonal, cardiorespiratory and behavioral changes occur in response to pain. The most important problem encountered when assessing pain in the newborn is the infant's inability to verbalize the pain response. Particular attention should be paid to nonverbal physiological and behavioral signs when measuring pain in infants (3). Painful procedures can negatively affect a newborn's adjustment to the external world (4). Starting from the first moments of life, it is the primary responsibility of the nurse to prevent the pain babies feel during painful procedures, and to help them cope with this pain (5). Other than the application of analgesics to reduce pain, nurses can also make use of

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non-pharmacological treatment methods. There are many non-pharmacological methods to reduce or eliminate the pain felt during interventional procedures. Among these methods are breastfeeding (6-7), the scent of mother's milk (8), the use of oral sucrose (9-11), skin-to-skin contact (3), kangaroo mother care (12,13), massage (14), and music (15). Another two effective methods are facilitated tucking (16-20) and white noise (21-24).

Sensitivity to touch develops in the 8th gestational week and by the 32nd gestational week, most of the baby's body becomes sensitive to even the light stroke of a feather (25). Sensitivity continues to grow significantly after birth. The primary method of communication for a newborn is, in fact, tactile contact. Gently touching a newborn can calm the baby and positioning the baby in the fetal position is conducive to both pacifying the infant through tactile stimuli and to allowing the baby to take the physiological position that will bring about the best protection (26). This method is therefore quite advantageous for these reasons. Facilitated tucking is the practice of holding the baby's arms and legs in a flexed position close to the midline of the torso, allowing the baby to move the extremities. Facilitated tucking may be used before invasive procedures, such as the heel-stick, to alleviate distress (5). The facilitated tucking position is one of the methods that involves touching and positioning the baby (27). Facilitated tucking aids the infant's ability to use the skills of self-regulation, such as bringing hands to mouth, grasping, or holding, so as to better cope with minor pain and stress (16,17,19,20,24,28). In Spain, facilitated tucking is a routine procedure for healthy neonates who were born in a hospital and are accompanied by their mothers during blood sampling (19).

Music is a very effective stimulant in relieving newborn pain. Audible alarms effectively distract the baby's attention, providing a cognitive strategy to control pain and suppress the pain response (29). Since white noise is a continuously monotonous sound in the form of a hum, it resembles the sounds in the mother's womb. Neonates are sensitive to white noise, which has a wide frequency spectrum (23,30,31). It is believed that fetal hearing develops before the 28th week of pregnancy (32). The baby in the intrauterine environment hears the reflected sounds of the mother's heartbeat, the sounds of her gastrointestinal system, the sounds made by the amnionic fluid as it joggles around inside the uterus, as well as sounds that are audible from the outside environment (33). It is known that following birth, rediscovering the abdominal sounds and rhythms of a mother has a relaxing and calming effect on a neonate. Experimenting with musical sounds does not only satisfy a newborn's emotional needs, but also provides feelings of safety and comfort (34). There is evidence in the literature that intrauterine sounds reduce stress, anxiety and pain and have a soothing effect on the fetus/baby and that these sounds positively affect the infant's physiological state (21,23,30,31). The common point in both methods examined is the effort to provide the the baby with the environment of the mother's womb.

There are no comparative studies in the literature that provide data as to which one of the two methods is more effective or about the effect of the combined application of these two methods on pain. Hence, our study was performed to identify the effect of white noise, facilitated tucking, and their combined application during heel-stick sampling on the level of pain in healthy term babies.

Materials and Methods

Study Design

The study was designed as a randomized clinical trial conducted at a single medical center. The design of the randomized experimental research is shown in Figure 1 (35).

Sample and Procedures

The criteria for inclusion in the study were: being a term baby, being with the mother, being a healthy baby who was being fed orally, having been fed at least half an hour before the procedure, not having received analgesics and/or sedatives within the last 24 hours, not having any complications that would prevent pain evaluation (e.g. intracranial hemorrhage, neuromotor growth retardation), not having undergone any painful procedures within the last hour (e.g. blood drawing, aspiration, ophthalmologic examination), having no prior history of surgery, not being connected to mechanical ventilation, and being able to draw the baby's blood on the first try (since the pain level can change on the second try).

The babies who met the study criteria and whose mothers gave informed consent were stratified according to their gestational age and then randomization was performed by casting lots. Three slips of paper of the same quality, size and thickness were marked as "white noise", "facilitated tucking" and "white noise + facilitated tucking," then folded and placed in a cloth bag. A health worker other than the researcher was asked to draw the slips and an equal number of babies were assigned to each group using the blocking method.

Sample Size and Power

The study sample size was determined by the free software G* Power (Version 3.1. 9.2 by Franz Faul, University of Kiel, Kiel, Germany: 2014). In the power analysis that was performed prior to the study, the pain score variable cited in the study by Karakoç and Türker (23) was used. This power calculation (with β=0.14087 and α=0.05 risk, Power=0.85913) determined that 27 neonates should be included in each of the three groups. To account for attrition within the groups, the target sample for each group was inflated to achieve a total of 90 babies (n=30 facilitated tucking; n=30 white noise; n=30 white noise and facilitated tucking) (Figure 1).

The accessible population comprised 105 term neonates who were born healthy between July 1, 2017 - August 9, 2017, at the hospital in which the study was performed. The sample comprised 90 healthy term babies from the population who met the criteria for inclusion in the sample and whose mothers gave consent.

Procedures

Prior to the data collection, a researcher provided the mother of the neonate with information about the study and answered her questions. The researcher took the babies' anthropometric measurements (height, head, and lenght) before the blood draw with a tape measure and recorded the results. As suggested by the literature (3,12,36-39), the mothers were left with their babies for 30 minutes before the start of the study to engage in kangaroo care. Following this, the babies included in the study were transferred to the procedure room, which is a dimly lit, tranquil room, for the venipuncture procedure. The mothers were also taken into the room with the baby. This was performed between 05:00 a.m. - 07:00 a.m. when the environment is at its most quiet. The study was conducted by a total of 3 people, two nurses and one of the researchers. One of the nurses drew the blood. The other evaluated the pain independently of the researcher. Each baby's heel blood was drawn by the same nurse, and each baby's facilitated tucking was performed by the same researcher. The same nurses took part in the study each time. The nurse who would conduct the Neonatal Infant Pain Scale (NIPS) scoring was familiarized with how NIPS was to be measured. The nurse who would perform the heel-stick sampling was reminded of the technique to be use.

The neonates included in the study comprised three groups. These were the group listening to white noise, the group placed in the fetal position, and the group to which both were applied (fetal position + white noise). Blood was drawn from the lateral left heel of the infants in all three groups. The same type of needle-No. 21-was used in the procedure. The blood drawing procedure was performed for all the babies with the same technique, the same nurse and at the same physical conditions of the room setting. Additionally, a 70% alcohol solution was used. Only the babies whose blood could be drawn at the first try were taken into the study.

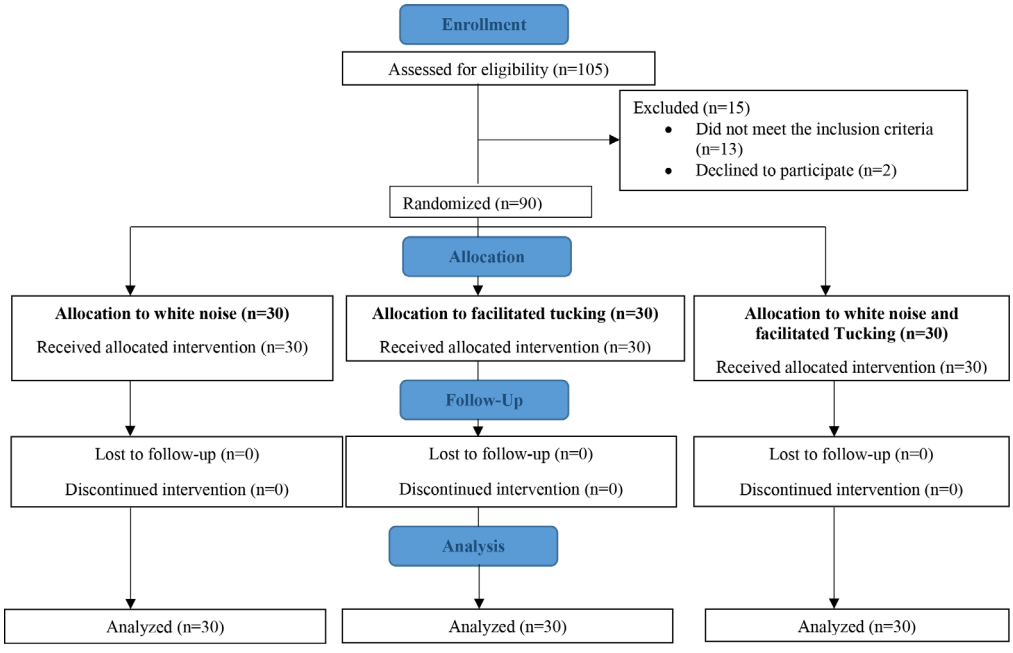

Figure 1. CONSORT flow diagram

Before the procedure, the researcher performed and recorded a respiration count for the babies. Additionally, a pulse oximeter was attached to the baby's right foot and the peak heart rate (PHR) and SpO_2 values were recorded. In each of the 3 groups, the researcher and the neonatal nurse independently scored the pain levels of the babies before the procedure according to NIPS and the results were recorded.

Experimental Group 1 listening to white noise. The babies listened to white noise produced with an X-brand MP3 player; an X-brand sound meter was used to measure the sounds and decibel levels of the environment. The sound meter was placed 50 cm away from the baby and the white noise sound level was adjusted to 55 decibels. Prior to the procedure, the baby's respiration was counted for 1 minute, after which a pulse oximeter was attached to the baby's right foot. The baby was then allowed to listen to the white noise for 2 minutes. During the procedure, the area from which the blood was to be drawn was wiped with the 70% alcohol solution and then left to dry for 30 seconds. Using a No. 21 needle, the experienced neonatal nurse drew the blood from the baby's left heel. The baby's respiration could not be counted during the procedure due to the baby's crying. The baby continued to be exposed to the white noise for one minute more after the blood draw had been completed. The researcher and the observing nurse each made an evaluation of the NIPS scores before, during and after the procedure.

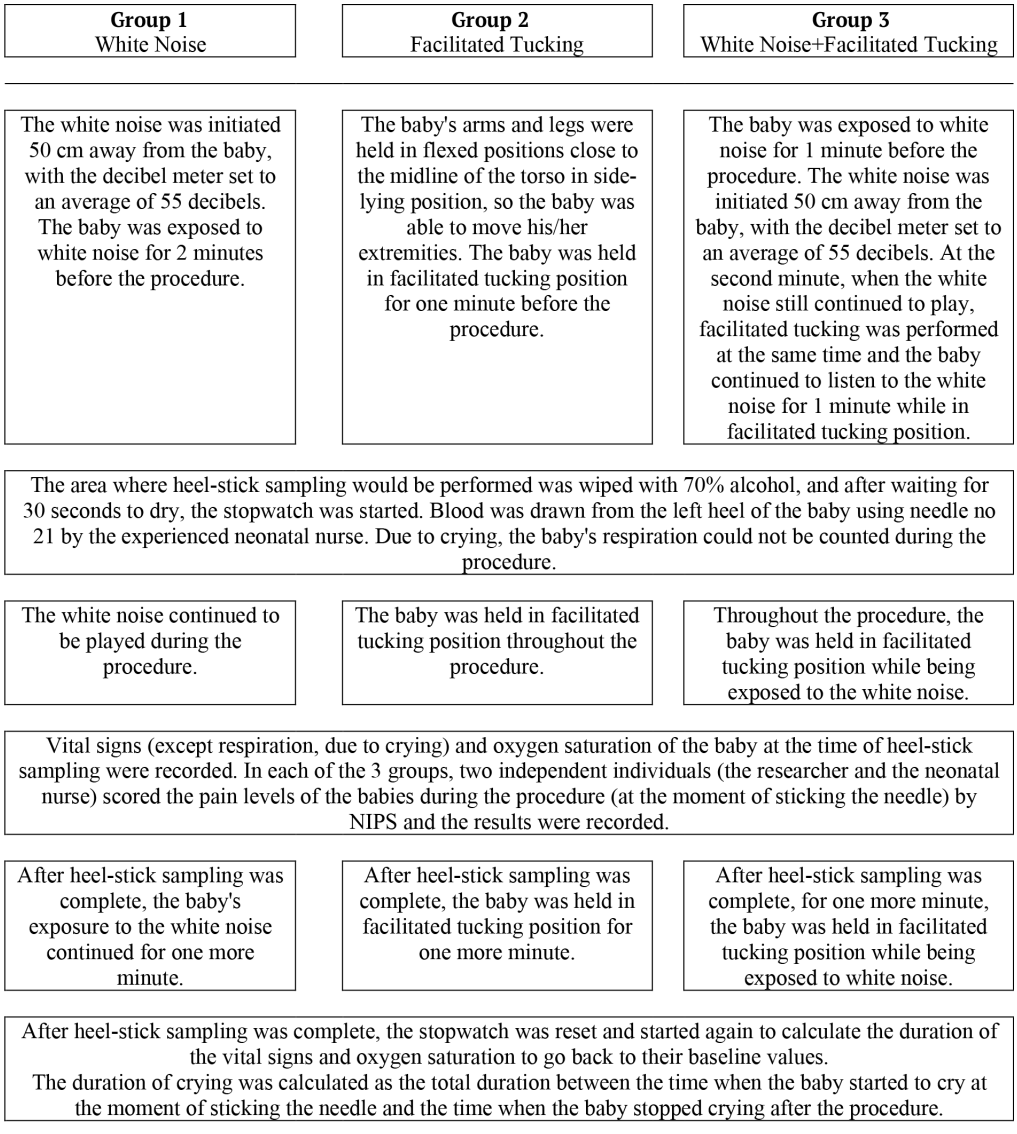

Figure 2. Research scheme

Experimental Group 2 placed in fetal position. The baby was placed lying on its side in the fetal position, with the upper and lower extremities manually flexed and positioned close to the body. The baby can move its extremities in this position. The baby's respiration was counted for one minute before the procedure and then a pulse oximeter was attached to the baby's right foot. The researcher held the baby in the fetal position for one minute and continued to hold the baby in this position during the procedure as well. The area from which the blood would be drawn from the heel was wiped with a 70% alcohol solution and left to dry for 30 seconds. Using a No. 21 needle, the experienced neonatal nurse drew the blood from the baby's left heel. The baby's respiration could not be counted during the procedure due to the baby's crying. The baby continued to be left in the fetal position for one minute after the blood draw had been completed. The researcher and the observing nurse each made an evaluation of the NIPS scores before, during and after the procedure.

Experimental Group 3 exposed to white noise + placed in fetal position. Prior to the procedure, the baby's respiration was counted for 1 minute, after which a pulse oximeter was attached to the baby's right foot. The baby was then allowed to listen to the white noise for 1 minute. At the start of the second minute, the baby was placed and kept in the fetal position for 1 minute and continued to be exposed to the sound of the white noise. Then, the area from which the blood was to be drawn was wiped with the 70% alcohol solution and left to dry for 30 seconds. Using a No. 21 needle, the experienced neonatal nurse drew the blood from the baby's left heel. The baby's respiration could not be counted during the procedure due to the baby's crying. The baby continued to be exposed to the white noise for one minute more after the blood draw had been completed. At the end of the procedure, the researcher/author and the nurse participating in the NIPS each made their own evaluation independently of each other.

The pain scores of the babies before, during, and after the procedure were independently evaluated by the researcher and the nurse who was not performing the heel-stick sampling. Cohen's kappa test was used to test the consistency of the scores given to the same situation by the nurse and the researcher in the evaluation of the NIPS pain scores. The ratings of the two individuals are completely compatible (Kappa Coefficient=0.953, p=0.027) (Figure 2).

Instruments

Data Collection Tools

A "Neonatal Introductory Information Form", "Data Evaluation Form" and the "NIPS" were used in the collection of data.

The Neonatal Introductory Information Form was developed by the researchers based on the literature (17,23,40). This form contains questions about the baby's characteristics.

The Data Evaluation Form includes questions about the neonate's PHR before, during and after the procedure, oxygen saturation, respiration rate, NIPS score, duration of the procedure, duration of crying, and the time required for the recovery of the peak heart rate, respiration, and oxygen saturation.

NIPS was used in the evaluation of the neonates' pain. This scale was developed by Lawrence et al. (41) (1993). The validity and reliability of the Turkish version of the test were assessed in 1999 by Akdovan (42), who reported Cronbach's alpha coefficient of consistency to be 0.83 during a vaccination procedure. Cronbach's alpha was 0.75 in the treatment group and 0.88 in the control group during the procedure. There are six variables related to the baby in the scale, namely, facial expression, crying, breathing patterns, arms, legs, and state of arousal. These variables are scored between 0-1. Only crying is scored between 0-2. The total score is between 0-7. The resulting score is directly proportional to the severity of the pain. That is, as the score increases, the severity of the pain increases.

The "white noise" used in our study is a fragment taken from the second part of the "Kolik" (Colic) album of Buzuki Orhan Osman, which has been used in similar studies (23,30). Orhan Osman and Neslihan Osman developed the white noise based on Dr. Harvey Karp's "The Happiest Baby," which comprises womb sounds. Orhan Osman performed frequency adjustments on these sounds and also added his own compositions under the various frequencies. An MP3 player and an X-brand decibel meter were used to measure the sound level that would be used in exposing the babies to the white noise. The decibel meter was placed 50 cm away from the baby and the white noise level was set to 55 decibels on average.

Statistical Analysis

Data were analyzed by using the International Business Machines (IBM) Statistical Package for Social Sciences (SPSS 21) (IBM Corp. Released 2012. IBM SPSS Statistics for

Windows, Version 21.0. Armonk, NY: IBM Corp.) statistical package programs. The normality of data was evaluated with the Shapiro-Wilk test for goodness of fit. Categorical data were expressed as frequency (n) and percentage (%). Continuous data were described in medians (Q1-Q3). Comparisons of the three groups (methods) were performed with the Kruskal Wallis-H test for non-normally distributed data. The Monte Carlo Chi-square test was used for the analysis of the cross tables created. For paired comparisons, the Mann-Whitney U test was used for non-normally distributed data. Spearman's correlation analysis was used to determine the relationship between two variables with non-normally distributed fit. The statistical significance level was accepted as $p<0.05$.

Ethical Approval

This study was approved by the Clinical Research Ethical Committee, of Eskişehir Osmangazi University Medical Faculty (approval date/number: 30.06.2017/80558721/188/01). Only babies from parents who gave their informed consent were included in the study. All protocols conformed to the ethical guidelines of the 2013 Helsinki Declaration. In addition, the aim of the study was explained, and written and oral permission from the mothers was obtained. The required permissions were obtained for the NIPS scale and the white noise album used in this study.

Results

All of the babies included in the study were term infants, accompanied by their mother; their overall condition was good, and they did not have any prior history of surgery. Babies who were admitted to the neonatal intensive care unit for various reasons (hyperthermia, respiratory distress, hyperbilirubinemia) were excluded from the study. Only two invasive procedures had been previously applied to any of the babies in our study was. These invasive interventions were IM vitamin K administration immediately after birth and an IM Hepatitis B injection. The babies in our study had not been given analgesics or sedative drugs in the last 24 hours and had not undergone any painful interventions in the last hour. The infants were fed within the last half-hour before the heel-stick sampling. All the babies included in the sample were fed orally. This allowed homogeneous distribution of the variables among the study groups.

Table I and Table II presents neonatal characteristics and inter-group similarities. It was found that there were no significant differences between the groups in terms of these characteristics, and the groups were similar ($p>0.05$). Sixty-four (71.1%) of the babies in the study were breast fed, 24 (26.7%) received breast milk + formula, and 2 (2.2%) were only fed formula (Table I).

Table III provides data on some of the physiological parameters and the NIPS scores of the neonates before the procedure. No significant differences were found between the groups in terms of PHR and NIPS before the procedure, and the groups were similar ($p>0.05$). There was a significant difference between the white noise group and the facilitated tucking group in terms of the respiratory and oxygen saturation rates of the neonates before the procedure ($p<0.05$). However, the respiration and oxygen saturation of the neonates in all groups before the procedure was within normal limits.

A comparison of the NIPS scores of the neonates during the procedure can be seen in Table IV. Table IV shows PHR, oxygen saturation and crying measures during the procedure, along with inter-group comparisons. The pain score of the group that listened to white noise and had been placed in the facilitated tucking position during the application was significantly lower than in the other two groups ($p<0.001$). Moreover, the pain score of the white noise group was significantly lower than in the facilitated tucking group. In this study, procedural peak heart rates were higher in the facilitated tucking position group ($p<0.05$) and a significant difference was detected between the groups in terms of total duration of crying ($p<0.001$). The group with the shortest duration of crying was the group that had listened to white noise and been simultaneously placed in the facilitated position. Furthermore, the duration of crying was longer in the facilitated tucking group than in the white noise group. No difference was found in this study between the oxygen saturation rates of the newborns during the procedure ($p>0.05$).

Discussion

One of the primary responsibilities of nurses working in neonatal units is pain management in infants. Various non-pharmacological interventions have demonstrated efficacy in preventing and relieving pain in infants undergoing painful procedures (43,44). It is important that these methods are effective, low-risk and cost-effective (45).

Various factors such as gestational age, gender, mode of delivery, nutrition and diet are important in pain perception and pain response in infants (46). It was found in this study that there were no significant differences between the groups in terms of these characteristics, and the groups were similar ($p>0.05$). Sixty-four (71.1%) of the babies in

the study were breast fed, 24 (26.7%) received breast milk + formula, and 2 (2.2%) were only fed formula (Table I).

Physiological symptoms such as heart rate, blood pressure, breathing pattern, and oxygen saturation are used to assess pain caused by acute procedures (46). In this study, no difference was found between the peak heart rates, respiratory rates and oxygen saturation rates of the newborns before the procedure (p>0.05). However, post-procedural peak heart rates were higher in the facilitated tucking group (p<0.05). According to synactive theory, the facilitated stretching position is a non-pharmacological pain modality that helps infants conserve energy, feel safe, calm themselves, and reduce oxygen consumption (47,48). To reduce the pain of the neonate during heel-stick sampling in our study, we found that the combined application of white noise and facilitated tucking was the most effective method of pain control (p<0.001) (Table IV). No studies were found in the literature on the effect of the concerted

Table I. Neonatal characteristics and their inter-group comparison (n=90)

Variables		White noise		Facilitated tucking		White noise + Facilitated tucking		Total		Statistics†	p-value
		n	%	n	%	n	%	n	%		
Gestational age	38 weeks	10	33.34	10	33.33	10	33.33	30	100.00	0.001	1.000
	39 weeks	10	33.34	10	33.33	10	33.33	30	100.00		
	40 weeks	10	33.34	10	33.33	10	33.33	30	100.00		
Mode of delivery	Vaginal	7	30.40	4	17.40	12	52.20	23	100.00	5.724	0.057
	Cesarean sect.	23	34.30	26	38.80	18	26.90	67	100.00		
Sex	Female	16	34.80	15	32.60	15	32.60	46	100.00	0.089	0.957
	Male	14	31.80	15	34.10	15	34.10	44	100.00		
Mode of nutrition	Mother milk	20	31.30	23	35.90	21	32.80	64	100.00	1.969	0.795
	Mother milk + formula	9	37.50	6	25.00	9	37.50	24	100.00		
	Formula	1	50.00	1	50.00	0	0.00	2	100.00		

†Monte Carlo chi-square

Table II. Postnatal age and anthropomorphic measurements of the neonates at the time of birth and inter-group comparison (n=90)

Variables			n	Median (Q1-Q3)	Statistics‡	p-value
Postnatal age (days)		White noise	30	2.00 (1.00-3.00)	3.504	0.173
		Facilitated tucking	30	2.50 (2.00-3.00)		
		White noise + Facilitated tucking	30	2.00 (1.00-3.00)		
Birth	Weight (gr)	White noise	30	3435.00 (3007.50-3558.75)	3.011	0.222
		Facilitated tucking	30	3130.00 (2952.50-3495.00)		
		White noise + Facilitated tucking	30	3340.00 (3007.50-3527.50)		
	Length (cm)	White noise	30	50.00 (49.00-50.00)	0.101	0.951
		Facilitated tucking	30	50.00 (49.00-50.25)		
		White noise + Facilitated tucking	30	50.00 (49.00-50.00)		
	Head circumference (cm)	White noise	30	35.00 (35.00-36.00)	1.904	0.386
		Facilitated tucking	30	35.00 (35.00-36.00)		
		White noise + Facilitated tucking	30	35.00 (35.00-35.00)		
		Facilitated tucking	30	32.00 (32.00-33.00)		
		White noise + Facilitated tucking	30	32.00 (32.00-33.00)		

‡Kruskal-Wallis H

Table III. Respiration, peak heart rate, oxygen saturation and nıps scores of the neonates before the procedure and inter-group comparison (n=90)

Variables		n	Median (Q1-Q3)	Statistics‡	p-value	Multiple comparison
Respiratory	White noise	30	58.00 (56.00-58.50)	8.570	**0.014**	1-2
	Facilitated tucking	30	56.00 (54.00-56.50)			
	White noise + Facilitated tucking	30	56.00 (55.50-58.50)			
Heart rate	White noise	30	135.00 (130.00-140.00)	1.435	0.488	
	Facilitated tucking	30	138.00 (131.50-140.00)			
	White noise + Facilitated tucking	30	135.00 (130.00-140.00)			
Oxygen saturation (%)	White noise	30	97.00 (97.00-98.00)	10.884	**0.004**	1-2
	Facilitated tucking	30	98.00 (98.00-98.00)			
	White noise + Facilitated tucking	30	98.00 (97.00-98.00)			
NIPS score	White noise	30	0.00 (0.00-0.00)	0.001	1.000	
	Facilitated tucking	30	0.00 (0.00-0.00)			
	White noise + Facilitated tucking	30	0.00 (0.00-0.00)			

‡Kruskal-Wallis H
1=White noise; 2=Facilitated tucking; 3=White noise + Facilitated tucking

Table IV. NIPS scores, peak heart rates and oxygen saturations and crying of the neonate groups during the procedure and inter-group comparison (n=90)

Variables		n	Median (Q1-Q3)	Statistics‡	p-value	Multiple comparison
NIPS score	White noise	30	4 (3-4)	53.168	**<0.001**	1-2 2-3 1-3
	Facilitated tucking	30	4 (4-5)			
	White noise + Facilitated tucking	30	2 (2-3)			
Heart rate	White noise	30	165.00 (161.50-167.25)	40.584	**<0.001**	1-2 2-3 1-3
	Facilitated tucking	30	168.00 (165.75-173.25)			
	White noise + Facilitated tucking	30	160.00 (158.00-164.00)			
Oxygen saturation	White noise	30	90.00 (89.00-90.00)	2.261	0.270	
	Facilitated tucking	30	90.00 (90.00-92.00)			
	White noise + Facilitated tucking	30	90.00 (89.00-90.00)			
Total crying time/second (during procedure + after procedure)	White noise	30	79.00 (71.75-90.00)	42.874	**<0.001**	2-3 1-3
	Facilitated tucking	30	80.00 (73.75-85.50)			
	White noise + Facilitated tucking	30	56.00 (50.00-62.50)			

‡Kruskal-Wallis H
1=White noise; 2=Facilitated tucking; 3=White noise + Facilitated tucking

application of these two methods on pain. However, several studies on the pain caused by interventional procedures performed on neonates (16-18) showed that facilitated tucking was effective whereas other studies (22-24,49) indicated that white noise was effective. The result of our study is important since we demonstrated that the combined application of white noise and facilitated tucking during heel-stick sampling is more effective than the use of either one of the methods alone. In another study, Ren et al. (49) examined the clinical effect of white noise applied together with glucose on reducing the procedural pain of retinopathy screening in premature infants, finding that the use of white noise in combination with glucose reduced procedural pain and stabilized vital signs in premature infants. This can be explained by the fact that when the neonate hears the accustomed sounds of intrauterine life, this establishes a sense of trust, reduces the neonate's stress, and calms the infant, thus reducing the effect of the pain produced by the intervention.

Another result of our study was that the pain score of the white noise group during heel-stick sampling was significantly lower than in the facilitated tucking group ($p<0.001$) (Table IV). Music is known to increase the release of endorphins and have a calming effect (50). Neonates are sensitive to white noise, which has a wide frequency spectrum (31). It is known that the baby is affected by maternal heartbeats even when still in the womb, and that hearing this familiar sound and rhythm after birth has a calming effect (30) and shortens the duration of crying (17,18,20). Facilitated tucking is a reliable, nonpharmacological method of reducing the acute pain of interventions (16-18,20). The reason behind this can be the release of endorphins produced after facilitated tucking is applied to the neonate. The literature reports that endorphins block the transmission of pain, preventing the stimulus from reaching the level of consciousness, and suppressing receptors such as histamine and brady quinine (50). The greater efficiency of white noise compared to facilitated tucking in reducing pain can be explained by the fact that the neonate's attention is focused on another stimulant other than the pain, thereby reducing the pain score. The results of our study are important as they demonstrate that in the event that both of these methods cannot be applied together, white noise should be preferred over facilitated tucking.

Pain can cause behavioral and physiological changes. In neonates, physiological parameters such as PHR, respiration and oxygen saturation as well as behavioral variables such as crying can be useful in the evaluation of pain that cannot be expressed orally (40).

Based on this information, the groups in our study were compared in terms of the PHR and oxygen saturation of the neonates during the procedure (Table IV). No significant difference was detected between the groups in terms of oxygen saturation during the procedure ($p>0.05$). Similar to our study, some other studies on facilitated tucking detected no differences in terms of oxygen saturation (17,20). In our study, a significant difference was detected between the groups in terms of PHR during the procedure ($p<0.001$). The group with the lowest PHR during the procedure was the group to which a combination of white noise and facilitated positioning was applied. There are no studies in the literature that compare these three groups. Moreover, in our study, the PHR value of the white noise group was lower than in the facilitated tucking group. Studies in the literature report that facilitated tucking reduces PHR during heel-stick sampling (17,20,28). Contrary to these results, however, in an experimental study by Liaw et al. (17) it was found that facilitated tucking during venipuncture did not have a significant effect on PHR, as compared to a control group that was under routine care. In the study by Karakoç and Türker (23), conducted to identify the effect on pain of holding, white noise, and the combined use of holding and white noise, it was found that the PHR value was lower in the white noise group than in the other groups.

One of the most important reactions to pain is crying (28). In our study, a significant difference was detected between the groups in terms of the total duration of crying ($p<0.001$) (Table IV). The group with the shortest duration of crying was the group that was exposed to white noise and simultaneously placed in the facilitated tucking position. Moreover, the duration of crying was longer in the facilitated tucking group than in the white noise group. In the literature, facilitated tucking is reported to reduce the duration of crying during heel-stick sampling as well as regulate the sleep-wake cycle after heel-stick (17,28). In the study by Balcı (30) with babies diagnosed with colic, it was found that 0-3-month-old babies who were exposed to white noise slept for a longer duration and cried/screamed for a shorter duration than the control group. In the study by Karakoç and Türker (23), Ren et al. (49), Kahraman et al. (22) and Cetinkaya et al. (21), the duration of crying and pain scores was shorter in babies exposed to white noise.

The results of the present study showed that in the group of babies to which a combination of white noise and fetal positioning was applied, crying durations, heart beats, respiration and oxygen saturation returned to normal in a significantly shorter period than in the other two groups.

In using these two non-pharmacological techniques in concert, the aim was to create an intrauterine environment for the baby. The outcome obtained may be associated with creating a comfortable and safe feeling for the baby during the heel-stick procedure by exposing the baby to both white noise that the infant can recognize and having the infant assume the fetal position, both of which are helpful to the baby in being more tolerant of the discomfort produced by the procedure.

It is accepted today that the heel-stick procedure is a significant source of pain for infants and may have a permanent effect. Compared to older children, infants may feel more pain in invasive procedures such as those performed with a needle. Depending upon the pain experienced, infants may exhibit short and long-term outcomes. Nurses should be aware of the pain caused by heel-stick sampling and accordingly use appropriate methods for pain relief. White noise and facilitated tucking are recommended as helpful options in cases where a method of pain control is required.

Study Limitations

A limitation of our study was that it included only term babies and the procedure of heel blood collection. The effectiveness of the study can be investigated in sick preterm babies as well.

A key limitation of the present study was the lack of blinding at any stage of the procedure and especially not in the assessment of outcomes.

The difficulty of our study was that the same three nurses were needed to perform the study the nurse who was one of the authors, another nurse to draw the blood, and a third to make the assessment. The procedure and the assessment should be carried out on the same day, but due to the nurses' shift schedules, the study could not be carried out on days when shifts did not coincide, which led to the prolongation of the work.

At the hospital where the study took place, no pharmacological or non-pharmalogical intervention is performed on neonates during the routine procedure of heel-stick blood sampling. It is important that studies on painful procedures in neonates include new methods that are implemented in addition to evidence-based techniques. The babies in our study were given kangaroo care for 30 minutes prior to the procedure. The fact that sucrose or breastfeeding was not applied to the newborns during the heel-stick sampling procedure is another limitation of the study.

Conclusion

One of our conclusions is that the concerted use of white noise and facilitated tucking during heel-stick sampling is more effective than the use of either one of these methods alone. Another conclusion is that the use of white noise to reduce the pain of the neonate during heel-stick sampling is more effective than facilitated tucking. Our suggestion is that these methods can be used in instances where family-centered care cannot be provided during heel blood collection. It is up to nurses to use the available evidence, to facilitate the involvement of parents, and to explore the best ways of improving care for newborns.

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Ethics

Ethics Committee Approval: This study was approved by the Ethical Committee of Eskişehir Osmangazi University Medical Faculty (approval date/number: 30.06.2017/80558721/188/01).

Informed Consent: Informed consent was taken from the participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.P., Concept: A.P., A.A., Design: A.P., A.A., Data Collection and/or Processing: A.P., Analysis and/or Interpretation: A.P., Literature Search: A.P., A.A., Writing: A.P., A.A.

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

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Original Article

Increasing Diagnosis Rates and the Changing Etiology in Childhood Pancreatitis; Ten Years of a Single-Center Experience in Turkey

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ABSTRACT

Aim: In this study, we aimed to evaluate the etiological, clinical, and laboratory characteristics of children with pancreatitis and the changes in these data over the years.

Materials and Methods: Children hospitalized with a diagnosis of pancreatitis between January, 2011 and January, 2021 were evaluated retrospectively. The etiology, demographic characteristics, laboratory findings, and changes over the years were analyzed.

Results: A total of 111 cases were enrolled, 72 (64.9%) in the acute pancreatitis (AP) group and 39 (35.1%) in the acute recurrent pancreatitis and chronic pancreatitis (ARP/CP) group. The most common causes of AP were idiopathic (27.8%), cholelithiasis (26.4%), and infections (8.4%). In ARP/CP assessments, idiopathic (35.9%), trauma (15.4%), and drugs (10.3%) were the most frequent etiologies. During the first five-year period, only 14 patients were diagnosed with pancreatitis, but in the second five years, 97 patients were diagnosed with pancreatitis. In both periods, the most frequent diagnosis was idiopathic pancreatitis (42.9% and 28.9%, respectively). While trauma (14.3%) and infections (14.3%) were the most common etiologies in the first five years, cholelithiasis (20.6%) and drugs (9.3%) were the most common in the second five years.

Conclusion: There was a significant increase between the first and the second five-year periods in pancreatitis-related hospitalizations. The most common cause of pancreatitis in all groups was still unknown. The cholelithiasis ratio increased from 7.1% to 20.6% in the second five-year period. Additionally, drugs played a bigger role in pancreatitis at a high rate of 9.3% over the years. Additionally, it was seen that the administration of octreotide treatment decreased over the years.

Keywords: Pancreatitis, etiology, child

Introduction

Over the last few years, pancreatitis has been increasingly diagnosed in children. Reports from different centers have shown that the incidence of childhood acute pancreatitis (AP) increased in the range of 0.78 to 13.2 annually per 100,000 children (1-5). Additionally, the incidence of pediatric chronic pancreatitis (CP) was 0.5-2 annually per 100,000 children and the prevalence was 6 cases per 100,000 children (6-8).

Pancreatitis is a clinical diagnosis based on a combination of history, physical examination, laboratory tests, and

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radiological findings. Thus, a significant increase in awareness plays a key role in the rise of pancreatitis incidence. As well as increased awareness among physicians, easily accessible serum amylase and lipase measurement and facilitated access to experienced radiologists undoubtedly provide for a rapid and accurate diagnosis of pancreatitis in children. Additionally, the definition of pancreatitis in children became clearer after the international pediatric pancreatitis working group (INSPPIRE) report, which has contributed to the increase in the number of patients diagnosed with pancreatitis (9,10). One study examined the changing frequency of AP across pediatric ages and characterized etiologies by age (11). As far as we know, this was the first report investigating and comparing the etiology, laboratory, and treatment modalities of pancreatitis in children over the years and it revealed an increase in pediatric pancreatitis referrals to tertiary care centers.

This study aimed to determine the trends of pediatric pancreatitis during the last decade at a tertiary care university-affiliated children's hospital and we hypothesized that the rate of pancreatitis in childhood increased over time.

Materials and Methods

This retrospective study was performed for all hospitalized children and adolescents (<18 years of age) diagnosed with pancreatitis at our institution between January, 2011 and January, 2021.

The patients' data were obtained from the electronic medical records of the hospital retrospectively and the analysis was limited to inpatient encounters and the first encounter with those patients with more than one admission for pancreatitis. Those patients whose data was unavailable or missing were excluded. The patients were categorized into two groups according to the international study group on pediatric pancreatitis: in search for a cure INSPPIRE; the AP group, and the acute recurrent pancreatitis (ARP) or CP (ARP/CP) group (10). All diagnoses were manually confirmed by a review of symptoms and signs at admission, along with laboratory, and imaging findings. The patients were evaluated in terms of their age, sex, body mass index (BMI) status by using Centers for Disease Control and Prevention criteria for pediatric-specific BMI percentiles, clinical findings, laboratory test results, radiologic findings, treatments, treatment responses, etiology of pancreatitis (as documented by the treating physicians), comorbidities and surgical procedures (12).

This study was approved by the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital (approval no: 2021/19-01, date: 09.12.2021).

Statistical Analysis

The data were assessed using descriptive statistics, including the numbers, percentages distributions, median, means, and standard deviations. Outcomes of interest were compared by the χ^2 test for categorical data. Student's t-test and Mann-Whitney U tests were used to compare continuous data which were distributed normally and non-normally, respectively. The total number of hospitalized patients was determined each year starting in 2011 and the incidence of pancreatitis among hospitalized patients was calculated annually. The data was evaluated via Statistical Package for the Social Sciences (SPSS) 20 (IBM SPSS Statistics for Windows, Version 20.0, released 2011; IBM Corp., Armonk, NY, USA). All p-values were 2-tailed, and $p<0.05$ was considered significant.

Results

There were 111 patients admitted for pancreatitis between 2011 and 2021. The median age at diagnosis was 11.0 years (1.0-17.0 years) and 54% of patients were male. The study group consisted of 111 children with 72 (64.9%) AP, 27 (24.3%) ARP, and 12 (10.8%) CP. Only one of the 12 CP cases was female, and the ratio of male to female patients was statistically significant in the CP group ($p=0.012$). Two patients from the CP group had a family history of pancreatitis but none of the AP or ARP cases had any family history. The demographic and clinical features of the patients are shown in Table I and the laboratory findings of the AP and ARP/CP groups are shown in Table II.

The most common causes of pancreatitis were idiopathic (27.8%), cholelithiasis (26.4%), and infections (8.4%) in the AP group. In the ARP/CP group, idiopathic (35.9%), trauma (15.4%), and drugs (10.3%) were detected most frequently (Table III). The rate of gallstones was higher in the AP group compared to the ARP/CP group (26.4% vs 5.1%, $p=0.006$). Two patients (1.8%) presented with pancreatitis and were diagnosed with primary pancreatic cancer, both with a negative family history of pancreatic cancer. The first one was a 15-year-old female with AP presentation of pancreatic neuroendocrine tumors, and the other was a 15-year-old male with CP presentation of an isolated pancreatic desmoid tumor.

The number of cases increased progressively from 14 to 97 between the first and the second five-year periods and

there was a significant increase (p<0.001) in pancreatitis-related hospitalizations over the years (Figure 1).

The demographic and clinical characteristics according to the first and the second five years are shown in Table IV. There was no statistical difference between these two periods in terms of laboratory test results, except for glucose (Table V). The median serum glucose levels were detected at 81.5 (6-221) mg/dL in the first five-year period, while it was higher in the second 101 (67-614) mg/dL (p=0.038).

The most common etiologies in the first five years were idiopathic (42.9%), trauma (14.3%), and infections (14.3%), while idiopathic (28.9%), cholelithiasis (20.6%), and drugs

Table I. Demographic and clinical features of the patients with pancreatitis

	Acute pancreatitis (n=72)	**Acute recurrent/Chronic pancreatitis (n=39)**	**p-value**
Gender (M/F) n (%)	38 (52.8)/34 (47.2)	22 (56.4)/17 (43.6)	0.714
Age (year) Median (min-max)	11 (1-17)	13 (1-17)	0.250
Clinical symptoms at admission n (%)	Abdominal pain 57 (79.1) Vomiting 11 (15.3) Fever 1 (1.4) Weight loss 3 (4.2)	Abdominal pain 31 (79.4) Vomiting 6 (15.4) Fever 1 (2.6) Weight loss 1 (2.6)	0.945
Weight status at admission n (%)*	Underweight 5 (6.9) Normal weight 47 (65.3) Overweight 4 (5.6) Obese 16 (22.2)	Underweight 4 (10.3) Normal weight 29 (74.3) Overweight 3 (7.7) Obese 3 (7.7)	0.300
Family history n (%)	0	2 (5.9)	NS

*According to BMI percentile
BMI: Body mass index, min-max: Minimum-maximum, M/F: Male/Female, NS: Not significant

Table II. Laboratory findings of patients with pancreatitis

	Acute pancreatitis (n=72)	**Acute recurrent/ Chronic pancreatitis (n=39)**	**p-value**
Amylase (IU/L) Median (min-max)	613 (67-8,517)	743 (95-2,199)	0.576
Lipase (IU/L) Median (min-max)	588 (25-5,670)	518 (21-4,640)	0.619
Alanine aminotransferase (IU/L) Median (min-max)	28 (7-788)	15.5 (6-475)	0.076
Aspartate aminotransferase (IU/L) Median (min-max)	35 (14-1,020)	23.5 (14-471)	0.022
Gamma-glutamyl transferase (IU/L) Median (min-max)	33 (2.8-788)	15 (6-238)	0.312
Alkaline phosphatase (IU/L) Median (min-max)	168 (8.4-388)	206.5 (72-449)	0.885
Blood glucose (mg/dL) Median (min-max)	102 (70-236)	94 (5-186)	0.191
Plasma creatinine (mg/dL) Median (min-max)	0.6 (0.4-1.0)	0.7 (0.3-1)	0.280
Calcium (mg/dL) Median (min-max)	9.7 (7.6-11.4)	9.5 (7.6-10.3)	0.837
C-reactive protein (mg/L) Median (min-max)	0.9 (0.02-23)	0.47 (0.05-6.6)	0.077
White blood cell count (/mm³) mean ± SD	11,989±6,085	9,728±3,637	0.017
Hematocrit (%) Median (min-max)	38.2 (5.3-45.4)	39.2 (29.9-44.4)	0.259
Platelet count (×10⁹/L) mean ± SD	358,500±3,866	286,480±1,370	0.264

min-max: Minimum-maximum, SD: Standard deviation

Table III. Etiology of pancreatitis			
	Acute pancreatitis frequency (n=72), n (%)	**Acute recurrent/Chronic pancreatitis frequency (n=39), n (%)**	**p-value**
Idiopathic	20 (27.8)	14 (35.9)	0.150
Gallstone	19 (26.4)	2 (5.1)	
Infections **Influenza** ***Salmonella*** **Coronavirus** **Mumps** ***Pneumococcal pneumonia*** **Tuberculosis**	6 (8.3) 2 (2.8) 1 (1.4) 1 (1.4) 1 (1.4) 1 (1.4) -	2 (5.1) - 1 (2.6) - - - 1 (2.6)	
Trauma	3 (4.2)	6 (15.4)	
Drug-related **Asparaginase** **Methylprednisolone** **Mercaptopurine** **Sodium valproate** **Colchicine overdose**	5 (6.9) 2 (2.8) 1 (1.4) - 1 (1.4) 1 (1.4)	4 (10.3) 2 (5.1) 1 (2.6) 1 (2.6) - -	
Hereditary ***SPINK1* gene positive** ***PRSS1* gene positive** ***CFTR* gene positive**	5 (6.9) 1 (1.4) 1 (1.4) 3 (4.2)	1 (2.6) - - 1 (2.6)	
Anatomic anomalies **Pancreas divisum** **Choledochal cyst**	3 (4.2) - 3 (4.2)	3 (7.7) 1 (2.6) 2 (5.1)	
Hypertriglyceridemia	4 (5.5)	2 (5.1)	
Autoimmune pancreatitis	2 (2.8)	-	
Duodenal bezoar	1 (1.4)	-	
Systemic disease **Familial Mediterranean Fever** **Type 1 diabetes mellitus** **Celiac disease** **Ulcerative colitis**	4 (5.5) - 1 (1.4) 1 (1.4) 2 (2.8)	3 (7.7) 1 (2.6) 1 (2.6) - 1 (2.6)	
Tumor	-	2 (5.1)	
PRSS1: Cationic trypsinogen gene, *SPINK1: Pancreatic secretory trypsin inhibitor* gene, *CFTR: Cystic fibrosis transmembrane conductance regulator* gene			

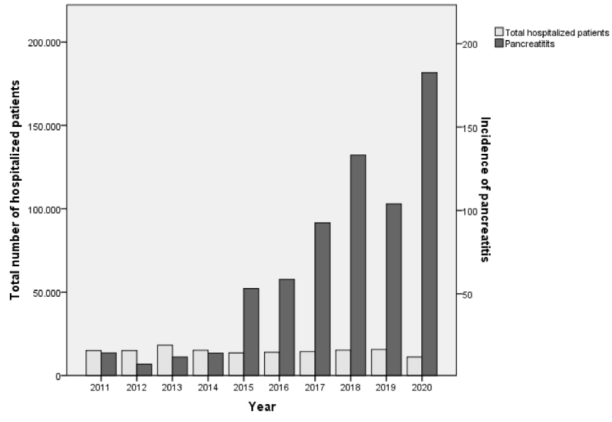

Figure 1. Incidence of pancreatitis among hospitalized patients. The 5-year incidence significantly increased in 2016-2020 compared to 2011-2015 (110.32/100,000 vs. 18.30/100,000; p<0.001; OR: 6.02, 95% CI 3.41-10.65)
OR: Odds ratio, CI: Confidence interval

Table IV. Demographic and clinical features of patients with pancreatitis over the years

	2011-2015 (n=14), n (%)	2016-2020 (n=97), n (%)	p-value
Gender (M/F)	10 (71.4)/4 (28.6)	50 (51.5)/47 (48.5)	0.163
Age (year) Median (min-max)	10.5 (1-16)	12 (1-17)	0.127
Clinical symptoms at admission	Abdominal pain 10 (71.4) Vomiting 4 (28.6) Fever - Weight loss -	Abdominal pain 78 (80.4) Vomiting 13 (13.4) Fever 2 (2.1) Weight loss 4 (4.1)	0.945
Nutritional status at admission	Underweight - Normal weight 13 (92.9) Overweight - Obese 1 (7.1)	Underweight 9 (9.3) Normal weight 63 (65.9) Overweight 7 (7.2) Obese 18 (18.6)	0.248
Family history	0	2 (2.1)	NS

min-max: Minimum-maximum, M/F: Male/Female, NS: Not significant

Table V. Laboratory features of patients with pancreatitis over the years

	2011-2015 (n=14), n (%)	2016-2020 (n=97), n (%)	p-value
Amylase (IU/L) Median (min-max)	405 (65-2294)	603 (11-8517)	0.653
Lipase (IU/L) Median (min-max)	970 (35-3270)	582 (21-5670)	0.506
Alanine aminotransferase (IU/L) Median (min-max)	46 (7-695)	22 (6-788)	0.577
Aspartate aminotransferase (IU/L) Median (min-max)	65 (18-542)	28 (8-1020)	0.139
Gamma-glutamyl transferase (IU/L) Median (min-max)	47 (4-831)	22 (2-811)	0.580
Alkaline phosphatase (IU/L) Median (min-max)	167 (104-399)	174 (8-594)	0.879
Blood glucose (mg/dL) Median (min-max)	81 (6-221)	101 (67-614)	0.038
Plasma creatinine (mg/dL) Median (min-max)	0.6 (0.3-0.8)	0.6 (0.3-1)	0.273
Plasma calcium (mg/dL) Median (min-max)	9.5 (7.6-10.3)	9.3 (7.6-9.7)	0.851
C-reactive protein (mg/L) Median (min-max)	0.4 (0.20-14.3)	0.5 (0.02-23)	0.653
White blood cell count (/mm^3) mean ± SD	12,356±7,712	11,025±5,104	0.452
Hematocrit (%) Median (min-max)	40.3 (29.9-48.3)	38.2 (5.3-48.4)	0.269
Platelet count (×10^9/L) mean ± SD	350,166±1,797	330,288±3,350	0.841

min-max: Minimum-maximum, SD: Standard deviation

Table VI. Etiology of pancreatitis over the years

	2011-2015 (n=14), n (%)	2016-2020 (n=97), n (%)	p-value
Idiopathic	6 (42.9)	28 (28.9)	0.810
Gallstone	1 (7.1)	20 (20.6)	
Infections **Influenza** ***Salmonella*** **Coronavirus** **Mumps** ***Pneumococcal pneumonia*** **Tuberculosis**	2 (14.3) 1 (7.1) - - - - 1 (7.1)	6 (6.2) 2 (2.1) 1 (1.0) 1 (1.0) 1 (1.0) 1 (1.0) -	
Trauma	2 (14.3)	7 (7.2)	
Drug-related **Asparaginase** **Methylprednisolone** **Mercaptopurine** **Sodium valproate** **Colchicine overdose**	-	9 (9.3) 4 (4.1) 2 (2.1) 1 (1.0) 1 (1.0) 1 (1.0)	
Hereditary ***SPINK1* gene positive** ***PRSS1* gene positive** ***CFTR* gene positive**	1 (7.1) 1 (7.1)	5 (5.2) 1 (1.0) 1 (1.0) 3 (3.1)	
Anatomic anomalies	-	6 (6.2)	
Hypertriglyceridemia	1 (7.1)	5 (5.2)	
Autoimmune pancreatitis	1 (7.1)	1 (1.0)	
Duodenal bezoar	-	1 (1.0)	
Systemic disease **Familial Mediterranean Fever** **Type 1 diabetes mellitus** **Celiac disease** **Ulcerative colitis**	- - - - -	7 (7.2) 1 (1.0) 2 (2.1) 1 (1.0) 3 (3.1)	
Tumor	-	2 (2.1)	

PRSS1: Cationic trypsinogen gene, *SPINK1: Pancreatic secretory trypsin inhibitor* gene, *CFTR: Cystic fibrosis transmembrane conductance regulator* gene

(9.3%) were most frequently detected in the second five years (Table VI).

The frequency of obesity was found to be 7.1% in the first five-year period, and it increased to 18.6% in the second five-year period. However, this rise was not statistically significant (p=0.248). Only 2 out of the 21 patients with gallstones were obese (9.5%), and no significant difference in the ratio of obesity was found between pancreatitis with gallstones or without gallstones (p=0.517).

There were 21 cases of gallstone pancreatitis in our cohort. The only significant difference in those patients with gallstones was observed with lower serum amylase with a median of 444 (95-1,857) IU/L compared to those without gallstones with a median of 706 (11-8517) IU/L (p=0.017), while all other laboratory data did not differ significantly.

Octreotide treatment was administered to 6 patients (42.9%) in the first five-year period and all these patients responded, while in the second five-year period, 11 patients (11.3%) were given octreotide and 81.8% of these patients were responsive.

Discussion

This study is one of a limited number of studies pointing out changes in pediatric pancreatitis in a tertiary children's hospital. We reported a significant increase in the incidence of pancreatitis among hospitalized children over the last decade at our hospital. Although the reasons for the increase in number of children with pancreatitis are not clearly understood, there are some possible explanations; namely, the clarification of the diagnostic criteria in pediatric pancreatitis, improved clinical awareness and improved access to imaging methods and laboratory facilities.

Another landmark of our study was the significant differences in the incidence and etiology of pancreatitis over the years. In the past decade, the rate of idiopathic cases decreased from 42.9% to 28.9%, but it was still the most frequent etiology in our center. Another pediatric study from Turkey reported similar findings in that the etiologic factors are still unknown in a quarter of patients, followed by systemic diseases in 14.3%, trauma in 11.1%, and cholelithiasis in 9.5% (13). A single-center study from Western China evaluated 130 children with AP and found that biliary tract disease (31.5%) and the idiopathic group (28.5%) were the most frequent etiologies, while a study from India with 320 children diagnosed with AP found that trauma (21%) and biliary tract disease (10%) were the most common causes (3,14).

In the past decade, we found that infections were the third most common cause of AP, but the rate of infections decreased from 14.3% to 6.2% in the second half of the decade. It was thought that the isolation and protection measures applied due to the coronavirus disease 2019 pandemic seen around the world could also have been effective in reducing the transmission of infection. This is still a very high rate when compared to previous pediatric studies with rates of 1.9-3.2% (5,13,15). Higher rates of viral infections were detected in Taiwanese, Chinese and Italian studies with rates of 10-12%, and this shows that etiology may differ according to geographical regions (14,16,17).

The high rate of drug-related pancreatitis (9.3%), which was the third most common cause in the second five-year period, may reflect the frequent use of asparaginase at our institution which has a high volume of oncology care. The fact that no drugs were included in the etiology in those cases in the first five years may be related to not sufficiently questioning drugs in their etiology. The third most common reason for the ARP/CP group was surprisingly drugs with a rate of 10.3%. The four (44.4%) out of the total 9 drug-associated ARP/CP patients were asparaginase-related. The reason for this high rate in ARP/CP patients may be the obligatory use of asparaginase in cancer treatment because of its important role in therapy. In the treatment of acute lymphoblastic leukemia, asparaginase is reported to cause pancreatitis in 5.3-7% of children (5,18).

While trauma is among the most common three causes in other studies, in our center, trauma ranks third with 14.3% in the first five-year period and it fell to fifth rank with 7.2% in the second five-year period. An Australian study had a higher number of AP associated with trauma (36%) compared to our study (15). This data was collected from a regional pediatric trauma and a major referral center for pediatric patients and that might explain the differences in results.

In our study, two patients (1.8%) who presented with pancreatitis were diagnosed with primary pancreatic cancer, both with a negative family history of pancreatic cancer. Smoking habits and possibly heavy alcohol use are elevating risks for pancreatic cancer as seen in pancreatitis in adult studies, and still slightly increased risk after CP was not ruled out (19). However, our patients did not have any alcohol or tobacco use in the past. Although pancreatic cancer is a rare disease, in a multicenter study with 246 patients from 10 countries diagnosed with hereditary pancreatitis at an early age (<30 years), a 3% prevalence of pancreatic cancer was found (20). For this reason, cancer should be considered in the diagnosis of childhood pancreatitis.

Gallstone pancreatitis represented a significant part of our cases with 20.6% over the years, consistent with previous reports which have shown that biliary tract disease is one of the top three causes of pancreatitis in children (3,4,14,21). Obstructive factors are more common in children than in adults (22). An increasing incidence of biliary pancreatitis has been reported due to increasing rates of obesity (21). With regards to this, only 9.5% of patients diagnosed with gallstones were obese and no significant differences in terms of obesity were detected in our study. The results of one pediatric study showed that aspartate transaminase (AST) was an independent predictor of biliary pancreatitis (21). There were 21 cases of gallstone pancreatitis in our cohort. The only significant differences in those patients with gallstone pancreatitis were observed with lower amylase, while lipase, AST, and the other laboratory data did not differ. Despite serum amylase levels remaining elevated for a shorter period compared to serum lipase after AP, it is surprising that lipase values did not differ (23,24). As regards laboratory findings, we found that the AST levels were significantly higher in those children with AP.

When comparing the first five years of laboratory data of our cohort with the second five years, blood glucose levels rose significantly over the years. Hyperglycemia and diabetes mellitus can occur with pancreatitis (25). An increase in the incidence of diabetes mellitus and obesity has been demonstrated globally in recent decades (26,27). As is well-known, hyperglycemia is often observed during AP (28). Additionally, hyperglycemia in CP patients is associated with reduced beta cell area (29). In our data, no significant difference in blood glucose levels was found between the AP and ARP/CP groups. Furthermore, blood glucose has

been correlated with complex high clinical and biochemical prognostic scores in some previous studies (30).

Study Limitations

Although the major limitations of our study are its single-center and retrospective design, it is an instructive study in revealing the nature of pancreatitis in children and addressing certain deficiencies in the diagnosis and management of these patients. Also, our study may be helpful as it provides the opportunity to notice changes in pediatric pancreatitis over the last decade.

Conclusion

This study has highlighted that the incidence of childhood pancreatitis has increased during the last decade (2011-2021) in our hospital. Most cases were idiopathic over this period, but the distribution of detectable etiologies and the tendency of octreotide treatment have changed. The risk factors, etiologies, clinical characteristics, and prognoses of many diseases change rapidly over the years. For this reason, dynamic analytical studies such as ours, in which new findings are evaluated and compared with those of previous periods, can play an important role in the literature.

Ethics

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of the University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital (approval no: 2021/19-01, date: 09.12.2021).

Informed Consent: Written informed consent was obtained from the patients and their parents.

Peer-review: Externally peer-reviewed.

Author Contributions

Surgical and Medical Practices: S.Ç., G.E., C.B.E., Ç.Ö.E., Ö.B., Concept: S.Ç., Ö.B., Design: S.Ç., Data Collection or Processing: S.Ç., N.P., Analysis or Interpretation: S.Ç., Literature Search: S.Ç., Writing: S.Ç., Ö.B.

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Original Article

Translation and Adaptation of the Existential Breastfeeding Difficulty Scale to Turkish

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ABSTRACT

Aim: Existential breastfeeding difficulty scale (ExBreastS) evaluates mothers who interrupt or terminate breastfeeding because of existential difficulties. Aim of the study was to adapt the scale for Turkish.

Materials and Methods: This methodological study was carried out between December 2021 and February 2022 in the obstetrics and gynecology clinic of a hospital in the west of Turkey. The study sample consisted of 139 mothers who fulfilling the study inclusion criteria. The data were obtained using a breastfeeding experience information form and the ExBreastS-Turkish form. Language adaptation and content validity, exploratory factor analysis, and confirmatory factor analysis (CFA) were performed to determine the validity of the scale, and internal consistency coefficient, item-total score correlation, split-half reliability, and test-retest analyzes were carried out to establish the reliability of the scale.

Results: An exploratory factor analysis showed that the instrument had a 3-factor construction with appropriate factor loads of the items (0.58-0.85). In addition, results of CFA showed that model fit indices of the instrument met the target values. Cronbach's alpha coefficient of the scale was 0.87, and the item-total score correlations ranged from 0.35 to 0.77. The test-retest correlation coefficient was 0.90 ($p<0.001$) and the Spearman-Brown reliability coefficient was 0.79.

Conclusion: The Turkish version of the ExBreastS evaluated in Turkish women showed that it was a valid and reliable measurement instrument after necessary corrections.

Keywords: Breastfeeding difficulties, existential, nursing, reliability, validity

Introduction

Breast milk is the best source of nutrition for all infants. Several medical and professional institutions strongly recommend exclusive breastfeeding for the first 6 months of life, followed by complementary and continuous breastfeeding (1,2). The World Health Organization (WHO) emphasizes that breastfeeding is beneficial for both the infant and the mother and strongly suggests the continuation of breastfeeding until at least the age of two (3).

Although the benefits of breastfeeding have been reported in several studies and several organizations have emphasized the importance of breastfeeding, results of the studies in Turkish women and the national data show that Turkish mothers do not follow global recommendations regarding the duration of breastfeeding (4). The WHO reported that approximately 44% of 0-6-month-old infants worldwide were exclusively breastfed over the period of 2015-2020 (5). National data from Turkey show that approximately 59% of 0-1-month-old infants are exclusively breastfed, but this rate decreases to 45% in 2-3-month-old infants and to 14% in 4-5-month-old infants (4). Therefore, breastfeeding has become a public health issue, and several studies have

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reported the biological, psychological, and social factors underlying early termination of breastfeeding (6-8).

Jean-Paul Sartre, who lived in 20th century, introduced the concept of "existentialism," which suggests that the existing is based on reality, that is, real existence, and is the opposite of essence. It is based on the fact that something exists, not what it is or how it is (9). Palmér et al. (10), with her existentialist interpretation of thought, has suggested that breastfeeding can be difficult for the mother and manifests itself in embarrassing feelings such as aversion to breastfeeding, aversion to the milk-producing body and anger at the infant.

Previous experiences of difficulties in breastfeeding may cause an existential trauma of breastfeeding in a woman's life (11). On the other hand, mothers with difficulties in breastfeeding have reported feelings of guilt and loneliness, causing them to have feelings of worthlessness and defeat. Existential anxiety and stress caused by breastfeeding difficulties are associated with other postpartum adjustment problems (12,13).

In Turkey, several breastfeeding inventories and psychometric tools are used to identify mother with breastfeeding issues and/or those who are at a risk of terminating breastfeeding at an early stage (14,15). However, to date, no scale is available to evaluate existential aspects of the breastfeeding difficulties among mothers. Therefore, this study aimed to adapt the existential breastfeeding difficulty scale (ExBreastS) into Turkish culture to examine the existential aspects of breastfeeding difficulties rather than their biological aspects such as insufficient breast milk production, clogged milk ducts, mastitis, and maternal fatigue.

Materials and Methods

Research Design, Setting and Relevant Context

A descriptive and methodological design was performed in the study. The study translation process and the Turkish adaptation process were carried out according to the International Test Commission Guide (16). The study was performed over a 5-month period in the Obstetrics and Gynecology ward of a university hospital in western Turkey. The results of the Turkey Demographic and Health Survey 2018 show that breastfeeding is quite common. Forty-one percent of infants under 6 months were exclusively breastfed, with a median breastfeeding period of 1.8 months for exclusively breastfed infants. The proportion of exclusive breastfeeding decreases rapidly with age. There is a sharp drop in the 4th month (4).

Sample

Mothers with 4-month-old infants were included in the sample because the sample selection favored a population with risk factors for breastfeeding discontinuation. The recommended sample size according to scale development and validity and reliability studies is 5 to 10 times the number of instrument items (17). In line with this recommendation, the study sample for this study consisted of 139 mothers.

Inclusion Criteria

- Mothers, who breastfeed their children at least once after birth,
- Mothers, who had healthy and full-term infants,
- Mothers, who no problems in communication,
- Mothers, who had internet access,
- Mothers, who volunteered to join in the study,
- Mothers, who submitted written consent.

Exclusion Criteria

- Mothers, who did not agree to join in the study,
- Mothers, whose children were born prematurely,
- Mothers, who were unable to communicate properly.

Measurement

Breastfeeding Experience Information Form: The form which was prepared by the researchers under the guidance of the literature, consists of 10 items, including sociodemographic features and information about the mother's breastfeeding experience (7,10,11,13).

ExBreastS: The ExBreastS was established by Palmér and Jutengren (18) to measure the existential aspects of the early breastfeeding challenges of the mothers. The questionnaire uses a 5-point likert-type scale (1=strongly disagree, 2=mostly disagree, 3=neither disagree nor agree, 4=mostly agree, 5=strongly agree) and consists of 16 items and has 3 subdimensions. Items that described positive aspects of breastfeeding challenges were reversed coded. The first subdimension, which has 7 items, is mother-child interdependency. The second subdimension, which has 5 items, is exposure and vulnerability and the third subdimensions, which has 4 items, is security and trust. The item-total score correlation of the scale is range from 0.37 to 0.82. A higher total scale score indicates that mothers have more existential breastfeeding difficulties. Permission was obtained via e-mail from Palmer, who developed the scale, in order to conduct this study.

Translation Process

The original version of the scale was translated from English to Turkish by a bilingual expert and two specialists

in pediatric nursing who fluent in English. Researchers examined the three translations and a linguist who had not seen the scale before translated the scale from English to Turkish. The researchers confirmed that no semantic shift was noted between the original version and the version back-translated into English. Finally, a single Turkish scale was obtained.

Content Validity Process

After the language equivalence was established, the Turkish versions of the instrument were presented to three pediatric nursing specialists, two gynecology and obstetrics nursing specialists, and two psychiatric nurse specialists to obtain their expert opinion regarding the content validity of the instrument. In order to determine the content validity of the scale, the opinions of seven experts were evaluated according to the Davis (19) technique. Content validity index (CVI) of the scale was found 1.0. After achieving a consensus among the experts, a pilot test was performed with 10 mothers. Mothers did not give any negative feedback about the instrument. The 10 mothers in the pilot study were exluded in the sample group.

Data Collection

The mothers who met the inclusion criteria during the postpartum period (between December 2021 and April 2022) were informed about the study by the researchers and their contact information was recorded after obtaining consent from the mothers. When the targeted sample size was completed, the survey prepared using Google forms were shared with all mothers online. During the study, mothers who had questions contacted the researchers and their questions were answered.

Statistical Analysis

The data were analyzed in the statistical package for the social sciences 21.0 program and analysis of moment structures 23.0 program was used for confirmatory factor analysis (CFA). Descriptive statistics for sociodemographic features and information about the mother's breastfeeding experience were presented as frequency, percentage, and mean. Turkish validity of the instrument was performed by exploratory factor analysis (EFA) and CFA. The suitability of the data for factor analysis was assessed using the Kaiser-Meyer-Olkin (KMO) test and Bartlett's sphericity test. We used the CFA to determine if the item and subscale described the original scale structure and looked at the model fit values. Cronbach's alpha coefficient, split-half analysis, item-total score analysis (Pearson correlation analysis), and test-retest analysis (test-retest reliability analysis performed with 15-day intervals in our study) were used for the reliability analysis of the instrument.

Ethical Considerations

Permission was obtained via e-mail from Palmer, who developed the scale, in order to conduct this study (18). Approval was obtained from the Non-Invasive Clinical Practices Ethics Committee of the Pamukkale University Faculty of Medicine, Department of Pediatric Nursing (approval no: E-60116787-020-143107 date: 14.12.2021). The study was performed under the guidance of the Declaration of Helsinki. Written informed consent was obtained from all mothers participating in the study after they were informed about the study.

Results

The mean age of the mothers and their infants was 29.33±4.25 years and 9.81±4.04 weeks, respectively. Among all mothers, 94.2% belonged to a nuclear family, 5.8% had an extended family, 78.4% had a bachelor's degree, 20.1% had a high school diploma, and 1.4% were primary school graduates. Additionally, 73.4% of the mothers were primiparous and 26.6% were multiparous. All mothers, except 5%, started breastfeeding within the first 24 h of delivery, 73.4% of them exclusively breastfed their infants, 22.3% of them fed their infants with a combination of both breast milk and formula, and 4.3% of them fed their infants only with formula. A total of 6 mothers stopped breastfeeding between the first and eleventh weeks of delivery.

Validity

Content Validity Index

CVI of the scale was found 1.0.

Construct Validity Analysis

EFA results showed a KMO score of 0.84 and a Bartlett's sphericity test score of $p<0.000$. The items explained 64.65% of the overall variance and were loaded on three factors with eigenvalues greater than 1.00, as in the original scale. We found that the factor loads of the items were between 0.58 and 0.85. As no factor load could be calculated for the two items in the original instrument, these two items were deleted from the Turkish version of the scale (Table I).

After all, 3 factors were modified in the model, the CFA showed a good fit for the data [$x^2=94.23$, degrees of freedom (df)=68, p=0.019, x/df 1.38] (Table II). The factor loads of the CFA model of the Turkish version of ExBreastS

Table I. Factor loading and analysis of the items of the existential breastfeeding difficulty scale			
Item No	**Factor 1**	**Factor 2**	**Factor 3**
Item 1	0.647	-	-
Item 2	0.750	-	-
Item 3	0.859	-	-
Item 4	0.802	-	-
Item 5	0.822	-	-
Item 6	-	0.807	-
Item 7	-	0.585	-
Item 8	-	0.754	-
Item 9	-	0.617	-
Item 10	-	0.686	-
Item 11	-	-	0.782
Item 12	-	-	0.814
Item 13	-	-	0.859
Item 14	-	-	0.689
Eigenvalue	5.580	2.053	1.419
Variance explained	39.855%	14.664%	10.133%
Rotation method: Varimax with Kaiser normalization			

Table II. Distribution of confirmatory factor analysis findings									
	χ^2/df	**RMSEA**	**GFI**	**NFI**	**RFI**	**CFI**	**RMR**	**IFI**	**TLI**
Model fit (modified)	1.386	0.053	0.910	0.906	0.902	0.971	0.032	0.972	0.962
Model fit (hypothetical)	2.092	0.089	0.864	0.846	0.811	0.912	0.044	0.913	0.891
Acceptance value	<5	<0.08	>0.90	>0.90	>0.90	>0.90	<0.08	>0.90	>0.90
χ2: Chi-square, df: Degree of freedom, RMSEA: Root mean square error of approximation, GFI: Goodness of fit index, NFI: Normed fit index, RFI: Relative fit index, CFI: Comparative fit index, RMR: Root mean square residual, IFI: Incremental fit index, TLI: Tucker-Lewis index									

ranged from 0.54 to 0.83 for the first factor, from 0.50 to 0.89 for the second factor, and from 0.63 to 0.88 for the third factor (Figure 1).

Reliability

The Cronbach's alpha value was found to be with 0.87 for the total instrument, 0.71 for the mother-child interdependency subscale, 0.83 for the exposure and vulnerability subscale, and 0.83 for the security and trust subscale. The results of the statistical analysis indicated that the test-retest correlation coefficient was 0.90 ($p<0.001$) (Table III). The item-total score correlations of the scale is presented in Table IV. Item-subscale total score correlation was ranged from 0.65 to 0.88.

Discussion

According to Davis (19) technique, the CVI score should be >0.80 (20). The CVI was >0.80 for this scale, so no scale item was removed, and all items were evaluated and necessary adjustments were made in line with the expert opinions. A high level of consensus has been reached between experts on ExBreastS.

Table III. Distribution of the reliability analysis findings				
	Scale total	**First sub-scale**	**Second sub-scale**	**Third sub-scale**
Cronbach α	0.873	0.713	0.837	0.836
First half of Cronbach α	0.786	0.725	0.772	0.786
Second half of Cronbach α	0.814	0.874	0.615	0.828
Spearman-Brown	0.793	0.778	0.758	0.762
Guttman split-half	0.783	0.742	0.751	0.757
Correlation between two halves	0.656	0.637	0.603	0.615
X ± SD (Min-Max)	23.00±8.106 (14-48)	6.09±1.97 (5-13)	9.36±4.42 (5-25)	7.53±3.41 (4-18)
Cronbach α: Cronbach's alpha, SD: Standard deviation, min-max: Minimum-maximum				

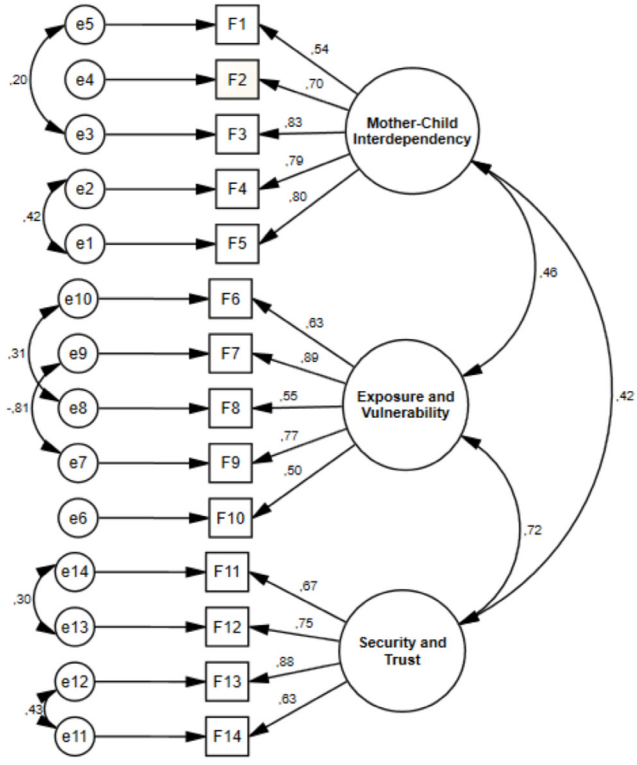

Figure 1. Confirmatory factor analysis results of three factor model

The KMO value was 0.84, suggesting that the sample size was sufficient for principal component analysis. Likewise, the results of Bartlett's test of sphericity (χ^2=965.55, p=0.000) showed that the variables were correlated and therefore satisfactory for EFA (21).

The EFA was conducted to determine the factor structure of the scale. The 3-factor structure of the scale explained 64.65% of the overall variance. The rate of explained variance for a measurement tool with validity and reliability should be at least ≥52% (22). Previous studies indicate that the factor load of each item should be ≥0.30. Items that factor load lower than 0.30 should be removed from the instrument. (23). In the light of this knowledge, items 6 "breastfeeding my child made my earlier times with them difficult" and 7 "I have reservations about adapting to my child's signals when I breastfeed them" were romeved from the instrument. The factor loads ranged from 0.58 to 0.85. Consequently, as a result of EFA were acceptable to decide the factor structure of the instrument.

Cultural adaptation studies recommend to conduct a CFA following EFA (24). CFA aims to determine the

Table IV. Correlations of item total score and item sub-scale total score

	X ± SD	Item-total score correlation (r)	Item-subscale total score correlation (r)
Mother-Child Interdependency			
1. Breastfeeding my child makes me feel like a failure as a mother.	1.33±0.78	0.355*	0.747*
2. I feel worthless when breastfeeding my child.	1.15±0.35	0.532*	0.654*
3. Breastfeeding my child makes me feel like I am worse than other mothers.	1.12±0.32	0.495*	0.720*
4. Breastfeeding my child prevents me from feeling joy for my child.	1.28±0.72	0.407*	0.730*
5. I think that my child feels like I am useless when I breastfeed them.	1.20±0.54	0.527	0.717
Exposure and Vulnerability			
6. I feel like I am stuck with breastfeeding my child.	1.61±0.99	0.738	0.826
7. I am tired of getting ready to breastfeed my child.	1.59±0.99	0.738	0.775
8. I feel like a machine when breastfeeding my child.	1.66±1.05	0.713	0.728
9. I do not always look forward to breastfeeding my child.	2.27±1.28	0.735	0.799
10. Breastfeeding my child makes me feel like it is my sole duty.	2.22±1.30	0.616	0.745
Security and Trust			
11. Breastfeeding my child fascinates me.	1.97±1.02	0.697	0.807
12. Breastfeeding my child makes me feel privileged.	1.78±0.99	0.698	0.836
13. I feel confident when I breastfeed my child.	1.78±1.00	0.772	0.889
14. I trust my body that it can produce enough milk to breastfeed my child.	1.98±1.13	0.646	0.754

SD: Standard deviation, p<0.05, *p<0.01

verification of the evidence regarding the adaptation of the tool in a different culture, and the results are evaluated through fit indices (25,26). On the basis of the results of the modification in the CFA analysis, the χ^2/df ratio was calculated as 1.38. This value was below 5, indicating an acceptable fit (Figure 1) (27).

For root mean square error of approximation (RMSEA) and resting metabolic rate (RMR), a value <0.08 shows an acceptable fit, while a value <0.05 indicates a perfect fit. The RMSEA and RMR values of the scale obtained in this study suggested a perfect fit. For other fit indices, a value >0.95 indicates a perfect fit, and a value >0.90 indicates an acceptable fit (27). In the current study, all fit index values were >0.90. Factor loads for each item in the CFA are required to be >0.30 (28). The factor loads of all items in this study were >0.30. Results of the CFA indicated that the data were compatible with the model, the 3-factor structure of the scale was confirmed as in the original, 3 factors were associated with the scale, and all items adequately described the factors to which they belonged.

Internal consistency, two-half reliability, and test-retest methods were performed to determine the reliability of the ExBreastS. In the original ExBreastS, the internal consistency coefficients of the factors were found to be 0.89, 0.86, and 0.73, which are similar to those in our study (18). In addition, the results of the test-retest reliability analysis performed with 15-day intervals in our study suggested that the scale was highly reliable over time (r=0.90, p<0.001). The predicted reliability of a scale should be at least 0.70 (29). In line with this information, the internal consistency coefficient and the Spearman-Brown reliability coefficient suggested that the Turkish version of the ExBreastS was a reliable measurement instrument.

In the original ExBreastS, the item-subscale correlations varied between 0.45 and 0.82. Scale validity and reliability studies emphasize that item-total and item-subscale correlations should be ≥0.30 to distinguish individuals from others in terms of the measured feature (30). In line with this information, the adapted ExBreastS had sufficient item-total and item-subscale correlations.

The reasons for interrupting or terminating breastfeeding are not always just physical. In this study, a scale that deals

with issues that may cause problems for breastfeeding due to existential difficulties has been adapted to Turkish culture. All healthcare professionals, especially pediatric nurses, can use this adapted scale as a screening tool for mothers in the postpartum period. As a result of screening, mothers at high risk for problems related to breastfeeding can be detected and the encouragement of breastfeeding can be provided by healthcare professionals.

Study Limitations

The data collected in this study were only from mothers who gave birth at a single hospital, and thus, the results of this study cannot be generalized to all Turkish women. The sociodemographic characteristics of the mothers in the sample group were similar to those of the Turkish women. Therefore, further studies are required to be performed to use this scale in mothers from different socioeconomic backgrounds and cultures and to confirm its suitability for Turkish culture.

Conclusion

This study determined that the Turkish version of ExBreastS consisted of 3 factors similar to those in the original scale. Unlike the original scale, the Turkish version of the scale eliminated two items because they because they were not applicable in the Turkish culture. Therefore, the Turkish version of the ExBreastS consisted of a total of 14 items. The internal consistency coefficient was high both for the total scale and subscales, reflecting cultural equivalence of the scale. The findings from this study showed that the Turkish version of the ExBreastS is a valid and reliable measurement tool for screening mothers with existential difficulties during breastfeeding.

Ethics

Ethics Committee Approval: Approval was obtained from the Non-Invasive Clinical Practices Ethics Committee of the Pamukkale University Faculty of Medicine, Department of Pediatric Nursing (date: 14/12/2021, approval no: E-60116787-020-143107).

Informed Consent: Informed consent was taken from the participants.

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Authorship Contributions

Surgical and Medical Practies: B.B., B.Ç., Concept: B.B., B.Ç., Design: B.B., B.Ç., Data Collection and/or Processing: B.B., Analysis and/or Interpretation: B.B., B.Ç., Literature Search: B.B., B.Ç., Writing: B.B., B.Ç.

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Original Article

Attitudes of Parents Towards COVID-19 Vaccinations for Their Children: A Single-Center Cross-Sectional Study

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ABSTRACT

Aim: Vaccine hesitancy has recently grown worldwide, caused by misinformation generally. This study aimed to determine parental intention to vaccinate children against the coronavirus disease-2019 (COVID-19) and any factors associated with vaccination hesitancy.

Materials and Methods: This cross-sectional survey study was conducted in a general pediatrics outpatient clinic. The parents of 12 to 18 years old children who were admitted to the clinic between June and December, 2021 (n=819) were included in this study. They were asked about their intention to vaccinate themselves and their children. The vaccination status against COVID-19, hesitancy or willingness to vaccinate their children, and factors affecting the parents' thoughts regarding COVID-19 vaccines were the measures of this study.

Results: The vaccination rate of the parents was 70.3%, while parents' intention to have their children vaccinated was 69.0%. Most parents had awareness regarding COVID-19 vaccines (88.3%), and most parents (89.4%) stated that the vaccination was necessary for the COVID-19 pandemic. Parents who had a male child or younger child were inclined to be hesitant. The parents' beliefs about the necessity of vaccines, their awareness of COVID-19 vaccines, and their vaccination status against COVID-19 were identified as factors decreasing their hesitancy.

Conclusion: Parents' attitudes and vaccination status play a key role in their children's vaccination. Providing reliable information to parents regarding COVID-19 vaccines should be considered a priority in order to increase childhood immunization.

Keywords: COVID-19, intention to vaccination, parents' attitudes, vaccination in children, vaccine hesitancy

Introduction

The coronavirus disease-2019 (COVID-19) is a severe infectious disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus which first emerged in Wuhan, China, in December, 2019 (1). The World Health Organization (WHO) declared COVID-19 to be pandemic disease on the 1th of March, 2020. Large numbers of people (over 500 million cases) had suffered from COVID-19 and 6.2 million patients had died from COVID-19 worldwide as of April, 2022. More than 15 million people had been infected with SARS-CoV-2 at the time of writing and nearly 100,000 deaths occurred in Turkey (WHO COVID-19 Dashboard. Available at: https://covid19.who.int/, accessed on the 26th April, 2022). Therefore, since transmission occurs predominantly via airborne droplets, preventive strategies such as keeping a physical distance of at least 1 meter from others, avoiding crowds and close contact, wearing

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a properly fitting mask, and keeping hands clean with alcohol-based hand rub or soap have been strenuously recommended by health communities worldwide.

Vaccination also plays a vital role in the fight against infections, especially during pandemics. Vaccines have dramatically reduced the rate of infectious diseases and deaths caused by them since their introduction (2). Nowadays, it is thought that vaccines reduce the severity and mortality of COVID-19 and the transmission of SARS-CoV-2 (3,4). The side effects of the vaccines have been stated in studies as being broad-spectrum but tolerable and low severity (3,5,6). As a severe side effect, myocarditis is prominent; however, it is commonly reported as mild to moderate and with quick recovery (7,8). Although the COVID-19 incidence and disease severity in childhood are lower than in adults, childhood vaccination has been proposed and applied in order to provide more effective control of the disease spread and provide herd immunity (4). After having approved the emergency use of mRNA vaccine (the Pfizer-BioNTech) in children 12 years of age and older by the Food and Drug Administration (FDA) in May, 2021 (FDA Authorizes Pfizer-BioNTech COVID-19 Vaccine for Emergency Use in Adolescents in Another Important Action in the Fight Against the Pandemic. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-pfizer-biontech-covid-19-vaccine-emergency-use.), immunization against COVID-19 in all children of these ages was also recommended by the Centers For Disease Control and Prevention (CDC), and the American Academy of Pediatrics (9). After the CDC and WHO recommendations, in Turkey, children 16 to 18 years of age started to vaccinated in July, 2021, and those aged 12-15 years started to be vaccinated in September, 2021.

Vaccine hesitancy is the most critical and biggest problem in childhood vaccination programs. This issue has recently grown worldwide and has been included in the list of ten threats to global health in 2019 by WHO (World Health Organization, Ten threats to global health in 2019. Available at: https://www.who.int/news-room/spotlight/ten-threats-to-global-health-in-2019. Accessed on the 28th of February, 2022). Lack of confidence was indicated as a critical reason, caused by misinformation, especially regarding the COVID-19 vaccination (10). Due to the fact that vaccination is a remarkable life-saving method, the causes of vaccine hesitancy should be considered in order to take measures and so increase the vaccination rate of COVID-19.

The primary objective of this cross-sectional study was to identify parental intention or hesitancy to have their children vaccinated and to assess factors associated with vaccine hesitancy. The second aim was to detect the parents' awareness regarding COVID-19 vaccines and their thoughts about vaccine necessity.

Materials and Methods

Subjects and Study Design

This cross-sectional study was conducted as a survey from July to December, 2021. A questionnaire was prepared online and in written format, and parents were asked to fill out the survey. The parents of 12-18 years old children filled out the form, and the data of eight hundred and nineteen parents who filled out the survey sufficiently were analyzed. The participants whose responses to the questionnaire were insufficient and/or conflicting were excluded from this study. The study was conducted according to the World Medical Association Declaration of Helsinki. Informed consent to participate in this study was taken from all children and their legal guardians via e-mail or in writing, and the Ethical Review Committee of the Ege University Faculty of Medicine approved the study (approval number: 21-8T/7).

Survey Design

The questionnaire included both written answers and multiple-choice questions. The survey consisted of three main domains: 1) Demographic data, 2) Parents' attitudes and behavior regarding the COVID-19 vaccination, and 3) Hesitancy or willingness regarding COVID-19 vaccines.

The "Demographic data" part included seven questions for the parents: the child's age, gender, their immunization status (for the routine schedule according to the National Immunization Program), their type of residential area, and the parents' education level (both the mothers' and the fathers'), and whether healthcare workers (HCWs) were among their nuclear family members.

The second part, entitled "Parents' attitudes and behavior regarding the COVID-19 vaccination", includes four questions. The survey asked whether the parents have information about the vaccines for SARS-CoV-2 and follow the news about COVID-19. Another question in this part asked what the parents thought about the necessity of COVID-19 vaccines and their reason. Potential causes (separately for each answer; "necessary" and "unnecessary") were listed in this part of the survey, and they were asked to choose one of them.

In the third part, "Hesitancy or willingness regarding COVID-19 vaccines", there were three questions. First, the

parents were asked about their immunization status against COVID-19. They were asked to choose "yes" if they had been fully vaccinated. In this study, the participants were considered "fully vaccinated" if the subject had received two vaccine doses as the booster dose had not been applied when we conducted this study. Other questions were about their children. The survey asked parents whether they had decided to vaccinate their children. If they answered "yes", they were asked which vaccine (BioNTech-Pfizer/Germany or CoronaVac, Sinovac/China) they would prefer.

Statistical Analysis

All data were analyzed using the inclusion body myositis (IBM) statistical package for the social sciences 25.0 software package (IBM Corp., Armonk, NY, USA), and p-values <0.05 were considered statistically significant. The quantitative variables which did not exhibit normal distribution were reported with median and interquartile range (IQR), and categorical variables were shown as frequencies and percentages. Univariate associations between the parents' vaccination status or willingness to have their child vaccinated and the various potential affecting factors were tested via the chi-squared test (pearson chi-squared and Fisher's exact test). We used a logistic regression model to identify the unique contribution of relevant factors affecting the vaccination of children. Variables significantly associated with study outcomes in univariate analyses were included in the regression analyses.

Results

A total of 819 parents completed the survey. The median age of subjects was 14.77 years (IQR=3.18); 68.6% of children (n=562) were 12-16 years old, and 51.0% (n=418) were female. The demographic data of participants are shown in Table I.

Most parents had awareness regarding COVID-19 vaccines (n=723, 88.3%) and stated that they followed news bulletin about COVID-19 (n=710, 86.7%). Most parents (89.4%) thought vaccination was necessary for the COVID-19 pandemic. The views on the reasons for the necessity of COVID-19 vaccines for parents are summarized in Table II. The most common reason was "vaccination provides mild relief from disease" (43.2%) among those parents who thought that vaccines were necessary, and "I do not trust vaccines' content" (24.1%) was among others.

In this study, 576 participants (70.3%) stated they had been vaccinated with two doses. Five hundred and sixty-five parents (69.0%) were willing to vaccinate their children, while 254 (31.0%) were hesitant about vaccinating them against SARS-CoV-2. Most willing parents (n=497, 88.0%) indicated that they would choose the BioNTech-Pfizer vaccine for their children.

Univariate analysis showed that the parents' willingness or hesitancy was associated with children's gender and age, their own immunization status, and the presence of a HCW in their family (Table III). In addition, it was found that there was an association between the belief in the necessity of vaccines and the parents' intentions. When a logistic regression model was conducted with significantly associated factors to identify the unique contribution of the relevant factors [The model fit was good (Hosmer and Lemeshow test p=0.117, Negelkerke R^2=0.305; Omnibus X^2=199.672, df=6)]; it was determined that vaccine hesitancy was quite common in unvaccinated parents and in those whose child was younger (12-16 years) or whose child was male (p≤0.001, 0.007, and 0.007; respectively) (Table IV). In addition, it was determined that the parent's belief that the vaccine was necessary and the parents' awareness about vaccines reduced their risk of hesitation significantly (p≤0.001, and 0.002; respectively).

Discussion

This cross-sectional study, conducted between July and December, 2021, showed that parents mostly had been vaccinated against COVID-19, and a similar rate were willing to have their children vaccinated. The gender and age of the children and the parents' immunization status affected the parents' willingness or hesitation. This study also found that awareness of SARS-CoV-2 vaccines and the belief in the necessity of these vaccines were other subjective factors associated with vaccinating children.

Many studies have investigated the rates of parents' intentions to have their children vaccinated with SARS-CoV-2 vaccine before the beginning of the vaccination program. A review published in December, 2021 reported that parents' willingness rates range from 10.4% to 92%, with a median rate of 59.3% (11). Previous studies from Turkey also showed the same heterogeneity, with 10.4%, 28.9%, 36.3%, 38.4%, 73.9%, and 75% (12-17). A study conducted by Yılmazbaş et al. (12) showed a high intention to vaccinate children at the beginning of the pandemic, and another study reported the intention to vaccinate children in pediatrician parents at a high rate (13). Fortunately, it was determined that the intention was at the highest rate at 69.0% just after the beginning of the vaccination program for 12 to 18 years old children in our study.

The HCWs showed a higher willingness to vaccinate their children against COVID-19, although this was non-significant statistically. Similar to our study, two studies conducted in Italy and Turkey demonstrated more parental willingness to vaccinate children against COVID-19 in HCWs (16,18). Similarly, Akarsu et al. (15) from Turkey showed high acceptance of the COVID-19 vaccine in HCWs for themselves but not their children. However, another study showed that doctors and especially nurses had a lower acceptance rate of future COVID-19 vaccines for their children than in the general population (19).

In this study, it was determined that the age and gender of children were associated with parents' hesitancy to vaccinate them with the COVID-19 vaccine. Those parents who had younger children (12-16 years) tended to have less intent to vaccinate their children. Similarly, a recent study by Goldman et al. (20) revealed that children's median ages were associated with their parents' willingness to

Table I. Demographic data of children in the study group

Age (years), median (IQR[a])		14.77 (3.18)
Age group, n (%)	12-16 years	562 (68.6)
	>16 years	257 (31.4)
Gender, n (%)	Female	418 (51.0)
	Male	401 (49.0)
Resident area, n (%)	Rural	74 (9.0)
	Urban	745 (91.0)
Children immunization status, n (%) (according to the NIP[b])	Fully-vaccinated	761 (92.9)
	Under-vaccinated	58 (7.1)
Having an HCW[c] in the family, n (%)	Yes	143 (17.5)
	No	676 (82.5)
Mother education level, n (%)	Illiterate and elementary school	366 (44.7)
	High school and higher	453 (55.3)
Father education level, n (%)	Illiterate and elementary school	336 (41.0)
	High school and higher	483 (59.0)

[a]IQR: Interquartile range, [b]NIP: National immunized program, [c]HCW: Healthcare worker

Table II. Thoughts of parents on the necessity of COVID-19 vaccination

Necessary n (%) 732 (89.4)	Vaccination provides mild relief from disease	316 (43.2)
	Vaccination protects against getting ill	135 (18.4)
	Vaccination prevents death caused by COVID-19	126 (17.2)
	Vaccination positively affects public health	111 (15.2)
	No reason	44 (6.0)
Unnecessary n (%) 87 (10.6)	Mistrust in COVID-19 vaccines' content	21 (24.1)
	Mistrust on COVID-19 vaccines	13 (14.9)
	Worried about the side effects of COVID-19 vaccines	13 (14.9)
	Concern about unknown effects of COVID-19 vaccines	12 (13.8)
	Negatively affected by the news	7 (8.0)
	Production of COVID vaccines abroad	7 (8.0)
	Religious beliefs	1 (1.1)
	No reason	13 (14.9)

In the questionnaire, parents were asked what they thought about the necessity of COVID-19 vaccines and the reason for them. Potential reasons shown in the list were given in the survey, and they were asked to choose the priority one for them
COVID-19: Coronavirus disease-2019

Table III. Factors affecting parental willingness or hesitancy of vaccination against COVID-19 for their children

		Willingness n (%), 565 (69.0)	Hesitancy n (%), 254 (31.0)	p-value
Age of children	12-16 years	363 (64.6)	199 (35.4)	<0.001
	>16 years	202 (78.6)	55 (21.4)	
Gender of children	Female	305 (73.0)	113 (27.0)	0.012
	Male	260 (64.8)	141 (35.2)	
Resident area	Rural	47 (63.5)	27 (36.5)	0.286
	Urban	518 (69.5)	227 (30.5)	
Having an HCW[a] in family	Yes	110 (76.9)	33 (23.1)	0.024
	No	455 (67.3)	221 (32.7)	
Parents' COVID-19 vaccination status	Vaccinated	451 (78.3)	125 (21.7)	<0.001
	Unvaccinated	114 (46.9)	129 (53.1)	
Mother's education level, n (%)	Illiterate and elementary school	244 (66.7)	122 (33.3)	0.197
	High school and higher	321 (70.9)	132 (29.1)	
Father's education level, n (%)	Illiterate and elementary school	225 (67.0)	111 (33.0)	0.297
	High school and higher	340 (70.4)	143 (29.6)	
Parent's awareness about COVID-19 vaccines		522 (72.2)	201 (27.8)	<0.001
Following the news about COVID-19		493 (69.4)	217 (30.6)	0.477
Parents' beliefs that a COVID-19 vaccine is necessary		555 (75.8)	177 (24.2)	<0.001

[a]HCW: Healthcare worker, COVID-19: Coronavirus disease-2019

Table IV. Predictors of hesitancy in parents to receive the COVID-19 vaccine for their children

Variables	OR (95% CI)	p-value
Age group		
12-16 years	1.726 (1.162-2.563)	0.007
>16 years	-	Ref
Gender		
Male	1.617 (1.144-2.286)	0.007
Female	-	Ref
Having an HCW[a] in family		
Yes	0.670 (0.416-1.081)	0.101
No	-	Ref
Parent's awareness about COVID-19 vaccines		
Yes	0.455 (0.277-0.748)	0.002
No	-	Ref
Parents' beliefs that a vaccine is necessary		
Yes	0.058 (0.028-0.117)	<0.001
No	-	Ref
Vaccinated parents (against COVID-19)		
No	2.216 (1.531-3.209)	<0.001
Yes	-	Ref

[a]HCW: Healthcare worker, COVID-19: Coronavirus disease-2019, OR: Odds ratio, CI: Confidence interval

have then vaccinated. These findings indicate that the age of the children was one of the essential factors in the willingness of parents to vaccinate their children. Contrary to our outcomes, which are in agreement with several studies, since COVID-19 has mainly spread via transmission in schools, the acceptance of the vaccine by parents who were worried about the disease was higher in the 7-12 years age group in the study of Zhang et al. (21). With regards to gender, studies generally pointed out that individuals intend to vaccinate male children more (22-25). The inaccuracy of vaccine-associated infertility, which has also been mentioned in the past, has been observed for COVID-19 vaccines (26,27). In the current study, parents' hesitancy for vaccination against COVID-19 was interestingly higher for male children.

It has been identified that the parents' trust in COVID-19 vaccines plays a critical role in their intention to have their vaccinated in many studies (22,25,28-31). Moreover, a good relationship between the physician and the patient might dramatically reduce hesitancy regarding the COVID-19 vaccination during the vaccine explanation. In our study, the parents' belief in a necessity of the vaccine, which was stated as "vaccination provides mild relief from the disease", was the prominent factor in decreasing the hesitancy of implementation. The parents' education level has been one of the most curious issues for vaccination hesitancy since the early stages of the pandemic. Several recent studies reported that high education levels substantially increased parents' willingness to have their children vaccinated (15,31-34). However, we determined that neither the mother's education level nor the father's education level affected the hesitancy or willingness of the parents in our study. In addition to the education level, it is crucial to underline that sufficient and reliable knowledge about new viral vaccines increases vaccine acceptance in COVID-19 vaccines (11,33-35). Consistent with our hypothesis, our study found that those parents who knew about new viral vaccines were less hesitant to have their children vaccine against COVID-19. This situation suggests that we could increase child vaccinations by properly informing the parents.

As expected, the parents' vaccination status for COVID-19 was obviously associated with the intention of having their child vaccinated. Thus, in this study, unvaccinated parents (29.7%) were more hesitant to have their children vaccinated. When we concluded this study in one of the biggest cities in our country, which has high awareness, the vaccination rate in adults was 72.4% nationwide, similar to our account (70.3%). However, one of the critical points was that among the unvaccinated parents, 46.9% of those were willing to have their children vaccinated against COVID-19. This rate was 9.4% in Israel, 11.7% in the United States, and in another study in Turkey, only 4.2% (15,31,36). The rate in our study was much higher than in those other studies. As a possible explanation, it was thought that parents trusted vaccinations to protect their children against severe diseases. The other explanation was that they were accustomed to vaccinations due to other childhood vaccinations. Akarsu et al. (15) conducted a study during the early pandemic period in Turkey. At that time, vaccinations had not been started yet for either adults or children; therefore, the low rate might be attributed to a lack of vaccine confidence during this early period. As also shown in several studies, it was emphasized insistently that a trust in physicians' recommendations (25,31,33,37) and the safety of vaccines (11,22,28,34) may improve the willingness of parents to have their vaccinated.

Study Limitations

There were a few limitations in our study. This study was conducted as a survey study; therefore, we obtained the data as stated by the parents. Moreover, because these data showed the parents' attitudes and thoughts, they do not reflect the actual vaccination rates of their children.

Conclusion

Despite the mild disease severity in children, vaccination against COVID-19 is the most prominent protection factor in children against severe infection and it also provides herd immunity. The parents' attitudes and vaccination status play a key role in their children's vaccination. Therefore, the parents' awareness and thoughts about the necessity of the COVID-19 vaccines are essential in decreasing the hesitancy to have their vaccinated. Considering that parents mainly obtain misinformation from social media or their social environment, the importance of reliable information provided by pediatricians should be emphasized. Consequently, increasing trust in doctors by providing accurate and sufficient information should be the primary goal in order to increase childhood vaccination rates.

Acknowledgments

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Ethics

Ethics Committee Approval: The Ethical Review Committee of the Ege University Faculty of Medicine approved the study (approval number: 21-8T/7).

Informed Consent: Informed consent was taken from the participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.E.D., Ş.G., F.K., Z.K., Concept: B.E.D., Ş.G., F.K., Z.K., Design: B.E.D., Ş.G., F.K., Z.K., Data Collection or Processing: B.E.D., Ş.G., F.K., Z.K., Analysis or Interpretation: B.E.D., Ş.G., F.K., Z.K., Writing: B.E.D., Ş.G., F.K., Z.K.

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Original Article

Telemental Health Assessment of Adolescents During the COVID-19 Pandemic: A Follow-up Study

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ABSTRACT

Aim: This study aimed to understand how the pandemic has affected the mental health of adolescents with a previous psychiatric diagnosis.

Materials and Methods: Fifty-nine patients aged 12-18 years who had been previously followed up in the adolescent mental health unit were included in this study. The participants were interviewed via telephone between June-July, 2020 and December, 2020-January 2021. Their socio-demographic data, psychiatric diagnoses and the previous Clinical Global Impression (CGI) scores were obtained from the patient files. The clinical global follow-up scale was scored by the interviewing physician.

Results: Past CGI scores before the pandemic were significantly greater for those participants with more than one psychiatric condition (p=0.024). For those participants with more than one psychiatric condition, the difference between the CGI scores prior to the pandemic and during the early stages of the pandemic were significant (p=0.004). The total satisfaction scores for telepsychiatry services assessed via the telemedicine evaluation form were statistically higher for those participants with a single psychiatric disorder (p=0.023). The past and early pandemic CGI scores were found to be inversely correlated with the telemedicine evaluation form with r=-0.338, p=0.019, r=-0.353 p=0.014, respectively.

Conclusion: The present study offers a perspective for adolescent mental health during the pandemic, underlining the importance and caveats of healthcare delivery to the youth with mental health problems during lockdown.

Keywords: Child and adolescent psychiatry, COVID-19 pandemic, mental health, telemental health, telepsychiatry

Introduction

The coronavirus disease-2019 (COVID-19) pandemic has placed severe strains on mental healthcare services and its delivery worldwide (1-5). To control the transmission of the virus and prevent the exhaustion of healthcare resources, social distancing and quarantine measures were implemented across the globe. Anxiety towards an uncertain future created by a potentially mortal virus, and a marked disruption in the daily lives of the youth and adults alike created an immense burden on mental health (6,7). The closure of schools, special education and rehabilitation centers, and social skills groups are likely to cause psychological distress for children and adolescents with neurodevelopmental disorders (8,9). Mandated quarantine or the home confinement imposed on children and their caregivers might increase the risk of developing anxiety, depressive, stress and trauma-related conditions as well as relapses of existing psychiatric disorders (3,8,10,11).

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While promoting mental health is an essential aspect of dealing with the COVID-19 pandemic, allocating available resources to infectious diseases and pulmonary care has been unavoidable. The reallocation of resources, combined with precautions to curb the spread of the virus such as social distancing policies resulted in the abatement of inpatient psychiatry unit capacities and severe restrictions on or outright suspension of outpatient psychiatric services in certain areas (4). Telemental health, where available, has replaced outpatient clinics to meet the needs of the youth and adults with mental disorders and disabilities with promising results (12-14). The present study aimed to understand how the pandemic affected the mental health of adolescents with a previous psychiatric diagnosis during it's the onset and progression of the pandemic.

Materials and Methods

Study Design

Sixty-seven patients with an appointment in the adolescent mental healthcare Clinic during the early stages of the pandemic (June 30th-July 30th, 2020) during which social distancing, mandated curfew policies were introduced were recruited for this study. During this time, telemental health approaches were implemented, and a psychiatric interview was conducted via telephone. A parent of the patient was also interviewed. The interview was structured into three sections via a questionnaire prepared by the authors: an interview with the patient comprising psychiatric complaints and neurovegetative changes, which included questions pertaining to sleep and alimentation habits based on the patients' subjective experiences, an interview with the parent, and a clinical assessment translated into a composite CGI score and medical or behavioral intervention if necessary. The participants were reevaluated after 6 months (December 30th 2020-January 30th 2021). Eight participants were unable to be reached and were excluded from this study; a total of 59 participants were contacted for follow-up. Socio-demographic data, psychiatric diagnoses assigned according to the DSM-5 criteria and other medical information were gathered retrospectively from the patients' health records. A telemedicine evaluation form prepared by the authors was also implemented in order to assess the effectiveness of the telemental healthcare services provided. Informed consent was sought from all participants and their legal guardians.

Measures

Clinical Global Impression (CGI): CGI is a measure of psychiatric symptom severity and treatment response, utilized in various settings and multiple countries as an effective assessment of the severity of mental disorders (15).

Telemedicine Evaluation Form: This form was comprised the following five five-point Likert questions: "I was able to understand the clinician clearly during the telemental interview.", "The telemental interview was as good as in person interviews.", "I would be falling behind on my work/school/chores if the interview wasn't conducted remotely.", "My family is satisfied with telemental health services." and "I am satisfied with telemental health services." This form was prepared by the authors to assess the effectiveness of telehealth and the participants' satisfaction.

Ethical Considerations

Permission to conduct this study was obtained from the Ege University Medical Research Ethics Committee (28.05.2020-20-5.1T/2) and the hospital where the research was performed.

Statistical Analysis

Statistical analyses were conducted with International Business Machines Statistical Package for the Social Sciences statistics v25.0. The Shapiro-Wilk test was utilized to assess the normality of the distribution. Gender and comorbidities were assigned as independent variables and intergroup changes in CGI and sleep duration were assessed with the Mann-Whitney U test. Categorical variables of gender, comorbidities and changes in appetite were assessed with pearson's chi-squared test and are presented in cross-tabulation. Changes during the follow-up in paired samples were assessed with the Wilcoxon ranked sum test. All non-parametric tests were two-tailed, and p-values <0.05 were considered statistically significant for all statistical analyses.

Results

Of the 59 patients participating in our study, n=36 (61%) were female and n=23 (39%) were male. The mean age of all participants was 15.94 (±1.43) years with the minimum and maximum values being 12 and 18, respectively. The relevant sociodemographic data and psychiatric diagnoses of the participants are summarized in Table I.

Changes in appetite and alimentation habits were assessed and while n=27 (45.8%) reported no changes during either interview, n=32 (54.2%) reported an increase, decrease or irregularities in their eating habits compared

Table I. Socio-demographic data and psychiatric diagnoses of the participants

	Single psychiatric diagnosis (n=30)	**>1 psychiatric diagnoses (n=29)**	**Total number of patients (n=59)**
Age, mean, (SD)	15.7 (1.57)	16.20 (1.23)	15.94 (1.43)
Gender, n (%)			
Male	10 (33.3)	13 (44.8)	23 (39.0)
Female	20 (66.7)	16 (55.2)	36 (61.0)
Education, n (%)			
Primary education	3 (10.0)	3 (10.3)	6 (10.2)
Secondary education	27 (90.0)	26 (89.7)	53 (89.8)
Psychiatric diagnoses, n (%)			
ADHD	8 (13.6)	21 (35.6)	29 (49.2)
Conduct disorder	0 (0.0)	5 (8.5)	5 (8.5)
Major depressive disorder	7 (11.9)	17 (28.8)	24 (40.7)
Anxiety disorder	11 (18.6)	12 (20.3)	23 (39.0)
Specific learning disorder	0 (0.0)	4 (6.8)	4 (6.8)
Autism spectrum disorder	0 (0.0)	1 (1.7)	1 (1.7)
Obsessive-compulsive disorder	1 (1.7)	4 (6.8)	5 (8.5)
Post-traumatic stress disorder	1 (1.7)	0 (0.0)	1 (1.7)
Tic disorder	0 (0.0)	1 (1.7)	1 (1.7)
Enuresis	1 (1.7)	0 (0.0)	1 (1.7)
Communication disorder	0 (0.0)	1 (1.7)	1 (1.7)
Affective disorder	1 (1.7)	2 (3.4)	3 (5.2)
Psychosis	0 (0.0)	0 (0.0)	0 (0.0)
Conversion disorder	0 (0.0)	2 (3.4)	2 (3.4)
Panic disorder	1 (1.7)	0 (0.0)	1 (1.7)
Maternal age, mean (SD)	44.0 (4.84)	44.87 (6.42)	44.45 (5.67)
Maternal education (completed), n (%)			
None	0 (0.0)	1 (4.0)	1 (2.0)
Primary	11 (23.9)	12 (26.1)	23 (50.0)
Secondary	7 (15.2)	7 (15.2)	14 (30.4)
Tertiary	3 (6.5)	5 (10.9)	8 (17.4)
Paternal age mean (SD)	48.13 (5.60)	49.20 (7.33)	48.69 (6.51)
Paternal primary education, n (%)			
None	0 (0.0)	1 (2.2)	1 (2.2)
Primary	9 (19.6)	13 (28.3)	22 (47.8)
Secondary	7 (15.2)	6 (13.0)	13 (28.3)
Tertiary	5 (10.9)	5 (10.9)	10 (21.7)

n: Number, SD: Standard deviation, ADHD: Attention deficit hyperactivity disorder

to their previous psychiatric assessments. In contrast, n=31 (52.5%) patients reported stable appetite and feeding habits in the follow-up interview, and n=28 (47.5%) reported an increase, decrease or irregularities. Changes in sleep habits were assessed and n=19 (32.2%) reported no changes during their initial interview while n=1 (1.7%), n=10 (16.9%) and n=29 (49.2%) reported decreased, increased or irregular sleep (shifts in day-night cycles, mid-day sleep, staying up late and sleeping in etc.), respectively. An increase or decrease in the duration or irregularities in sleep patterns were reported by n=37 (62.7%) participants in the follow-up interview, with n=7 (11.9%), n=5 (8.5%), and n=25 (42.4%) reporting an increase in sleep duration, a decrease in sleep duration and irregularities in sleeping habits compared to the pre-pandemic period, respectively. Twenty-two participants (37.3%) reported no changes in their sleep patterns in comparison to the pre-pandemic period. The mean sleep duration in the early and later phases of the pandemic was 9.67 (±1.71) and 8.10 (±3.46) hours with median sleep durations being 10 and 9 hours, respectively. This difference was found to be statistically significant (p=0.041). The changes in alimentation and sleep habits during the early and late phases of the pandemic are summarized in Table II.

The median values of CGI for each period for those participants with a single psychiatric disorder (n=30) and those with more than one psychiatric condition (n=29) were compared. The CGI scores prior to the pandemic between the two groups were significantly greater for those participants with more than one psychiatric condition (p=0.036). However, no significant differences were found in the CGI scores in the early (p=0.847) or later stages (p=0.496) of the pandemic compared to the pre-pandemic period. Subsequently, changes in the CGI scores across the time periods in each group were separately analyzed. For those participants with a single diagnosed psychiatric disorder, no significant changes across the three designated time periods were observed. However, for those participants with more than one comorbid psychiatric conditions, CGI scores were conversely decreased following the pandemic, with the difference between the median CGI scores prior to the pandemic and during the early stages of the pandemic being significant (p=0.002). No significant differences in the CGI scores between the other periods were observed. The CGI scores of the participants, the differences among the groups and changes in the CGI scores over time are summarized in Table II and III, respectively.

The telemedicine evaluation form prepared by the authors was utilized to assess the participants' general satisfaction with telephone based telemental health. Of the 59 participants, 48 accepted to complete the telemedicine evaluation form via telephone. No item in the form was found to be statistically significant between those participants with a single or more than one co-occurring psychiatric disorder. However, the total satisfaction scores were statistically higher for those participants with a single psychiatric disorder (p=0.023). The telemedicine evaluation form and associated data are summarized in Table IV and V.

Table II. Changes in alimentation and sleep habits during the early and late phases of the pandemic

	Early pandemic				**Late pandemic**				
Neurovegetative habits, n (%)	**Regular**	**Increase**	**Decrease**	**Irregular**	**Regular**	**Increase**	**Decrease**	**Irregular**	**p-value**
Appetite/Alimentation habits	27 (45.8)	18 (30.5)	8 (13.6)	6 (10.1)	31 (52.5)	9 (15.3)	11 (18.6)	8 (13.6)	-
Sleep habits	19 (32.2)	10 (16.9)	1 (1.7)	29 (49.2)	22 (37.3)	7 (11.9)	5 (8.5)	25 (42.4)	-
Sleep continuance, mean (SD)	**Early pandemic**				**Late pandemic**				
Sleep duration (h)	9.67 (1.71)				8.10 (3.46)				0.04*

*p-values less than 0.05 were considered statistically significant
n: Number, SD: Standard deviation

Table III. The CGI scores of participants with a single and more than one psychiatric diagnoses

CGI scores	**Single psychiatric diagnosis (n=30)**		**>1 psychiatric diagnoses (n=29)**		**p-value**
	Median	**Mean (SD)**	**Median**	**Mean (SD)**	
Past CGI scores (Prior to the pandemic)	3.0	2.76 (0.23)	4.0	3.48 (0.23)	0.036*
CGI scores early pandemic	3.0	2.70 (0.20)	3.0	2.82 (0.17)	0.847
CGI scores late pandemic	3.0	2.70 (0.26)	3.0	3.07 (0.21)	0.496

*p-values less than 0.05 were considered statistically significant
n: Number, SD: Standard deviation, CGI: Clinical Global Impression

Table IV. The changes in CGI scores of participants over time

CGI scores	Single psychiatric diagnosis (n=30)	>1 psychiatric diagnoses (n=29)
	p-value	p-value
CGI past-CGI early pandemic	0.617	0.002*
CGI early-CGI late pandemic	0.869	0.307
CGI past-CGI late pandemic	0.696	0.159

*p-values less than 0.05 were considered statistically significant
n: Number, CGI: Clinical Global Impression

Table V. The telemedicine evaluation form satisfaction scores between those participants with a single and more than one psychiatric disorder

Telemedicine evaluation form items	Single psychiatric diagnosis (n=24)		>1 Psychiatric diagnoses (n=24)		p-value
	Median	Mean (SD)	Median	Mean (SD)	
1. I could easily hear the doctor during the telemedicine interview	4.0	4.37 (0.71)	4.0	4.04 (0.95)	0.193
2. The telemedicine interview was as good as a face-to-face interview	3.5	3.25 (1.03)	2.0	2.75 (1.07)	0.065
3. If it wasn't for telemedicine, I would have been behind on my school/work	2.0	2.70 (1.12)	2.0	2.45 (1.10)	0.356
4. My family is satisfied with telemedicine	4.0	4.08 (0.50)	4.0	3.83 (0.96)	0.463
5. I am satisfied with telemedicine	4.0	3.83 (0.70)	4.0	3.54 (0.88)	0.266
6. Telemedicine evaluation form total scores	18.0	18.25 (2.54)	16.0	16.62 (2.73)	0.023*

*p-values less than 0.05 were considered statistically significant
n: Number, SD: Standard deviation

The past and pandemic era CGI scores were found to be inversely correlated with the telemedicine evaluation form with r=-0.338 p=0.019, r=-0.353 p=0.014, respectively. The correlation between the CGI scores during the follow-up and the telemedicine evaluation form scores were found to be statistically non-significant (r=-0.243, p=0.097).

Discussion

The disruption of the daily routines of adolescents and their parents alike was significant in the present unprecedented health crisis of the modern era. Changes in daily routines brought with them changes in neurovegetative habits. A significant increase in sleep duration in the present study during the later stages of the pandemic without significant impairment in psychosocial functioning may be attributed to an increase in free time. This is in line with the extant literature as an increase in sleep duration was reported during school-closures resulting from the pandemic (16).

Significant difficulties in adjusting to online education were reported by the parents of those children with attention deficit hyperactivity disorder (ADHD) during the pandemic. ADHD and being part of an individualized education program seem to be among the challenges in the adaptation to remote learning during the COVID-19 pandemic, (17,18) especially for those children and adolescents with additional neurodevelopmental disorders (19,20). However, the increase in depressive and anxiety symptoms associated with the changes in daily living and support networks in the lives of children and adolescents during the pandemic should also be taken into account, especially for those youth with neurodevelopmental disorders, in the assessment of the mental effects brought about by the lockdown (21). While developmental disorders such as ADHD, depressive and anxiety symptoms all contribute to the deterioration of psychosocial functioning, an interesting finding of the present study, contrary to our hypothesis, are the changes in psychosocial functioning across time. While no significant changes in CGI scores were observed for those participants with a single psychiatric condition, a decrease in the CGI scores, marking an improvement in psychosocial functioning, was observed in the early stages of the pandemic for those youth with more than one comorbid psychiatric diagnosis. While an increase in psychiatric

symptoms in various settings during the pandemic was previously reported, a possible explanation of our results might be the alleviation of social and academic pressures during the pandemic, especially for those youth with the aforementioned developmental problems such as ADHD and depressive or anxiety symptoms/disorders. Suspension of in-person education facilities and the adoption of online education, combined with a marked reduction in the peer-related social pressures of adolescence might have relieved stress in those youth with good support systems in place (i.e., supportive and caring parents with established productive hobbies and pastimes), resulting in an overall improvement in their mental health and preventing the worsening of any previously diagnosed psychiatric conditions (22-24).

These findings are also in line with CGI scores increasing for the aforementioned group, albeit non-significantly from a statistical standpoint, as the later phases of the pandemic were marked with an increase in uncertainty towards the future, a possible increase in financial strains and the reintroduction of social and academic stresses with policies being implemented in favor of normalization i.e., schools reopening on certain days of the week along with academic examinations. A recent study from England reported an increase in self-rated emotional and functional difficulties as well as depressive mood after school re-openings during the COVID-19 pandemic (25). Similarly, an increase in psychiatric symptoms, diagnoses, and psychotropic medication use in youth was reported in several studies in the later phases of the pandemic. As such, better follow-up and assessment of those youth with existing psychiatric disorders is advised in order to minimize the possible distress and exacerbations this population might experience as the pandemic progresses (26,27).

Study Limitations

The major limitation of the present study is the small sample size. Although the pandemic itself imposed certain limitations on study design, further studies with an emphasis on prospective research with more sizable samples are needed to accurately assess the effects of the pandemic on mental health and the utility telemental approaches.

Conclusion

Different telemedicine approaches ranging from telephone-based interviews to videoconference calls were utilized before and during the pandemic (28,29). Our study provides an understanding into the lesser employed telephone-based telemedicine practices for psychiatric evaluation. While effective for follow-up purposes, the marked dissatisfaction of those youth with multiple comorbid psychiatric disorders may indicate that telephone-based telepsychiatry is inefficient in the assessment of those youth with complex psychiatric needs. However, the inverse correlation between the CGI scores and telemedicine satisfaction scores underlines a critical aspect of the pandemic for those youth with multiple psychiatric disorders. Our study highlights that those youth with lower prior and pandemic CGI scores were more satisfied with receiving the psychiatric help they required, although this association disappeared as the pandemic progressed.

Overall, the effects of the pandemic on mental health fluctuated across different time periods and varied for different cultures and populations. The present study offers a perspective for adolescent mental health across the pandemic for those adolescents with mental health issues prior to the pandemic. However, multicenter and nationwide population-based studies are needed to validate the results of the present study concerning the effects of the pandemic on adolescent mental health, as the data procured from a single tertiary adolescent mental health clinic does not represent the colorful and varied experiences of all adolescents during the pandemic.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Local Ethics Committee of Ege University Medical Research Ethics Committee (28.05.2020-20-5.1T/2)

Informed Consent: Informed consent was taken from the participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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Original Article

Factors Affecting Colchicine Adherence in Pediatric Familial Mediterranean Fever

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ABSTRACT

Aim: Familial Mediterranean Fever (FMF) is the most frequent monogenetic autoinflammatory disorder. It is characterized by fever and serositis. The first line treatment of FMF is colchicine. Adherence to colchicine is one of the main factors affecting colchicine response. In this study, we aimed to evaluate drug adherence in children with FMF using the medication adherence scale in FMF (MASIF). We also assessed the clinical characteristics of drug-adherent patients and factors affecting drug adherence.

Materials and Methods: Eighty-two children with FMF under colchicine therapy were included in this cross-sectional observational study. The patients were divided into two groups according to medication adherence and compared according to their demographic and clinical data.

Results: According to MASIF, 31 (38%) patients had non-adherence to colchicine. There was a significant difference between the colchicine-adherent and non-adherent groups in terms of age, disease severity according to the International severity score for FMF, attack rate, colchicine dosage, M694V homozygosity, and family type (p=0.005, p=0.04, p=0.025, p=0.045, p=0.04, and p=0.046, respectively).

Conclusion: Patients with FMF should be questioned about their medication adherence at every visit, and children with a high risk of colchicine non-adherence should be followed up more closely.

Keywords: Adherence, children, colchicine, familial mediterranean fever, non-compliance

Introduction

Familial Mediterranean Fever (FMF) is the most frequent monogenetic autoinflammatory disorder characterized by fever and polyserositis (1). It is caused by a point mutation in the *Mediterranean Fever (MEFV)* gene located on chromosome 16p13.3 encoding an immune regulatory protein, pyrin (1,2). In FMF, the mainstay of treatment is life-long colchicine use (2,3). However, up to 5% of patients are resistant to this medication (4). Adherence to colchicine is one of the main factors affecting colchicine response, and thus the long-term outcomes in patients with FMF (5,6). There are some scales developed to measure medication adherence. The Morisky medication adherence scale, developed as a self-report measure of antihypertensive medication adherence (7), has been used to evaluate adherence to drugs used for the treatment of many diseases, including FMF (8,9). In 2015, Yesilkaya et al. (10) developed the Medication compliance scale in FMF MASIF (Table I) to measure medication adherence specifically for pediatric patients with FMF. In the current study, we planned to investigate colchicine adherence in children with FMF using MASIF.

Materials and Methods

After the ethics committee approval was obtained from Manisa Celal Bayar University Faculty of Medicine, Health Sciences Ethics Committee (29.12.2021-20.478.486/1117),

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this cross-sectional observational study was conducted in February-April 2022 among the children who were diagnosed with FMF based on the pediatric criteria described by Yalçinkaya et al. (11) and treated with colchicine at our pediatric nephrology and rheumatology clinic. Informed consent was conducted from the parents/guardians of the patients. Patients using medication other than colchicine, those with cognitive dysfunction that would prevent them from completing the questionnaire, patients with proteinuria or amyloidosis, and those that were followed up for less than six months were excluded from the study. The demographical and socio-economic data, family history, number of attacks experienced within the previous year, and genetic mutation analysis of the patients were retrospectively assessed by screening the hospital database and patient files. The international severity score for FMF (ISSF) was used to evaluate disease severity (12). A total score of ≥6 was interpreted to indicate severe disease, 3-5 intermediate disease, and ≤2 mild disease. The Turkish version of MASIF (Table I) was completed by the parents/guardians of the patients under seven years old and by the patients themselves if they were over seven years. The participants responded to each of the 18 items on a Likert scale (1=strongly agree, 2=agree, 3=no idea, 4=disagree, 5=strongly disagree). A cut-off value of 60 points was accepted as good adherence for MASIF (10). The children were assigned into two groups according to medication adherence and compared demographically and genetically. The patients were given regular colchicine treatment (≤0.5 mg/day for patients under five years of age, 0.5-1 mg/day for five to 10 years, 1-1.5 mg/day for >10 years) (13).

Statistical Analysis

International business machines (IBM) statistical package for the social sciences statistics v. 26 was used for statistical analyses (IBM Corp., Armonk, NY, USA). Descriptive statistics were utilized as mean±standard deviation or median (minimum-maximum) values for measured data, and frequencies and percentages (%) for categorical data. The normality of the distribution of parameters was evaluated visually (histogram and probability graphics) and by analytical methods (the Kolmogorov-Smirnov and Shapiro-Wilk tests). Student's t-test or the Mann-Whitney U test was carried out to analyze the differences in continuous variables, while the chi-square test was used to compare categorical variables. The Kruskal Wallis-H test was performed to compare multiple variables. The association between the variables was assessed with

Table I. Medication compliance scale in FMF (MASIF)

No	Items
1	I know about my illness and I am aware that my treatment will continue for a long time.
2	I sometimes forget to take my medication.
3	I rely on the treatment prescribed for my disease.
4	I refrain from others when taking drugs.
5	Continuous drug usage affects my daily life.
6	When I am out of home (on vacations, travels, etc.) I forget to take my drugs.
7	I wish this disease had a treatment without drugs.
8	I sometimes do not take my drugs on time because of my daily routine.
9	I think my illness will get better if I use my drug regularly.
10	I know the adverse effects of the drug.
11	I need to be convinced to use my medication regularly, for a long time.
12	I'm afraid that continuous drug use may lead to other diseases.
13	If I leave my drug, my disease may worsen.
14	I could not get used to using my drug regularly.
15	When I realize that I forgot to take my medication, I take my drug even it is delayed, I do not skip doses.
16	When I disrupt my drug my complaints may increase.
17	I am tired of continuous drug use.
18	I think it is quite difficult to use medicine in multiple doses during a day.

MASIF: Medication adherence scale in FMF, FMF: Familial Mediterranean Fever

the Spearman correlation coefficient. A p-value of <0.05 was used for statistical significance.

Results

A total of 82 children (38 male, 44 female) with FMF were enrolled in this study (Table II). The mean current age of the patients was 13.5±4.5 years. The mean age at FMF diagnosis was 6.9±4.5 years. Fifty-five (67%) of the patients had a family history of FMF. Genetic mutation analysis was conducted in each patient with FMF. There were 19 patients with M694V homozygous mutations, 41 with heterozygous mutations (M694V mutation positivity in 18), and 12 with compound heterozygous mutations (M694V mutation positivity in 8). Ten patients (12%) had no mutation in the *MEFV* gene.

The clinical characteristics of the patients are presented in Table III.

According to ISSF, 40 (49%) patients had mild, 25 (30%) had intermediate, and 17 (21%) had severe disease. Sixty-

Table II. Demographic data of patients

Variables		**Patients (n=82)**
Age (Mean±SD)		13.5±4.5
Age at diagnosis (Mean±SD)		6.9±4.5
Gender (M/F)		38/44
Family history of FMF, n (%)		55 (67)
Severity according to ISSF, n (%)	Mild disease	40 (49)
	Intermediate disease	25 (30.5)
	Severe disease	17 (20.5)
Attack rate per month in the previous year, n (%)	<1 attack	62 (75.5)
	1-2 attack	11 (13.5)
	>2 attacks	9 (11)
Colchicine doses (median, min.-max.) (mg/day)		0.5 (0.5-1.0)
Living place, n (%)	Rural	8 (10)
	Urban	74 (90)
Family type, n (%)	Nuclear family	65 (79)
	Extended family	17 (21)
Social security, n (%)	Available	74 (90)
	Unavailable	8 (10)
Socio-economic status, n (%)	Low income	32 (39)
	Middle income	43 (52)
	High income	7 (9)
Employment status, n (%)	Schoolers	50 (80.5)
	Employed	13 (16)
	Unemployed	6 (7)
Smoking in patients, n (%)	Yes	6 (7)
	No	76 (93)
Alcohol use in patients, n (%)	Yes	3 (4)
	No	79 (96)
Substant use of patients, n (%)	Yes	0
	No	82

n: Number, SD: Standard deviation, FMF: Familial Mediterranean Fever, ISSF: International severity score for Familial Mediterranean Fever, M: Male, F: Female, min.: Minimum, max.: Maximum, MASIF: Medication compliance scale in FMF

two (75.5%) of patients had under 1 attack per month. The median colchicine dosage was 0.5 mg/day.

According to MASIF, 31 (38%) patients had non-adherence to colchicine (Table IV). Colchicine adherence was found to be decreased when the child grew older. There was a significant difference among the colchicine-adherent and non-adherent groups in terms of age, disease severity according to ISSF, attack rate, colchicine dosage, M694V homozygosity, and family type (p=0.005, p=0.04, p=0.025, p=0.045, p=0.04, and p=0.046, respectively). However, the two groups did not statistically significantly different in age at diagnosis, gender, family history of FMF, place of residence, socio-economic status, smoking status of patients, and alcohol use of patients (p=0.6, p=0.8, p=0.56, p=0.9, p=0.3, p=0.5, and p=0.3, respectively).

Table III. Clinical data of patients

Variables		**Patients (n=82)**
Severity according to ISSF, n (%)	Mild disease	40 (49)
	Intermediate disease	25 (30.5)
	Severe disease	17 (20.5)
Attack rate per month in the previous year, n (%)	<1 attack	62 (75.5)
	1-2 attack	11 (13.5)
	>2 attacks	9 (11)
Colchicine doses (median, min-max) (mg/day)		0.5 (0.5-1)

n: Number, min: Minimum, max: Maximum, ISSF: International severity score for Familial Mediterranean Fever

Table IV. The relationship between demographic and clinical characteristics of patients and colchicine adherence according to MASIF

	Colchicine adherent patients (n=51)	**Colchicine non-adherent patients (n=31)**	**p-value**
Age	12.5±4	15±4	0.005
Age at diagnosis	6.7±4.4	7.2±4.7	0.6
Gender (M/F)	24/27	14/17	0.8
Family history of FMF	33/18	22/9	0.56
Severity according to ISSF, n (%)			0.04
Mild disease	27 (53)	12 (39)	
Intermediate disease	17 (33)	7 (22.5)	
Severe disease	7 (14)	12 (39)	
Attack rate, n (%)			0.025
<1 attack	43 (84)	19 (62)	
1-2 attack	5 (10)	6 (19)	
>2 attacks	3 (6)	6 (19)	
Colchicine dose (median, min.-max.) (mg/day)	0.5 (0.5-1)	1 (0.5-1.0)	0.045
M694V homozygousity, n (%)	8 (16)	11 (35)	0.04
Living place, n (V/T/C)	4/24/23	3/13/15	0.9
Family type (N/E)	44/7	21/10	0.046
Socio-economic status (H/M/L)	5/28/18	5/15/14	0.3
Smoking in patients, n (%)	3 (6)	3 (10)	0.5
Alcohol use by patients, n (%)	1 (2)	2 (6)	0.3

FMF: Familial mediterranean fever, MASIF: Medication compliance scale in FMF, n: Number, M: Male, F: Female, ISSF: International severity score for FMF, min.: Minimum, max.: Maximum, V: Village, T: Town, C: City, N: Nuclear, E: Extended, H: High, M: Middle, L: Low

Discussion

In this study, we demonstrated the factors affecting colchicine adherence in children with FMF according to MASIF. We found that 38% of our patients were non-adherent to colchicine. Age, disease severity, the number of attacks experienced in the previous year, colchicine dosage, M694V homozygosity, and family type were determined to be statistically correlated with colchicine adherence in pediatric patients with FMF.

Colchicine is defined as the best treatment option for reducing attacks and preventing complications of FMF, such as amyloidosis (2,3). Colchicine treatment also avoids the use of alternative drugs; e.g., biological therapeutics and their side effects (12,13). Colchicine resistance is an important challenge in the management of FMF. It is known that adherence to colchicine is one of the main reasons for colchicine resistance (14). MASIF is a scale developed to measure medication adherence in pediatric patients with FMF. Using MASIF, Yesilkaya et al. (10) and Sönmez et al. (15) reported that 70% and 40% of their patients with FMF were colchicine non-adherent in their respective studies. Similarly, the results of the current research on MASIF indicated that 38% of the patients were non-adherent to colchicine among pediatric FMF cases. Tekgöz et al. (16) determined that 83.8% of adult patients with FMF were non-adherent according to the compliance questionnaire on rheumatology. Sönmez et al. (15) reported a higher adherence rate in younger children (5). The higher rate of non-adherence to medication in adolescent patients with FMF confirms that when patients get older, drug non-adherence increases, as also observed in the current study. Adolescent patients are more non-compliant with colchicine, this may be due to the refusal of medication by the adolescent to avoid side effects.

Children with severe disease and frequent attacks are required to take higher doses of colchicine to manage the disease. It is reported that patients with severe disease and frequent relapses have higher rates of colchicine non-adherence (15). Similarly, in the current study, it was determined that as the colchicine dose increased, the rate of colchicine adherence of the patients with FMF decreased. Öztürk et al. (17) and Barut et al. (18) showed that colchicine resistance was more frequent in patients with FMF who had M694V homozygous mutations. In the current study, we observed that the colchicine non-adherent patients had a higher rate of M694V homozygosity. Due to the frequent attack rate and higher colchicine dosage required to control the attacks of M694V homozygous patients, their colchicine adherence might be lower. Family and social support are considered to be crucial in drug adherence in chronic diseases (19-21). Living in a nuclear family is related to the effective management of many chronic diseases, including hypertension and human immunodeficiency virus, as well as health-related quality of life (20,21). In the current study, the children with FMF living in a nuclear family were determined to be more adherent to colchicine.

The use of tobacco and alcohol is known to be a factor for non-adherence to treatment in various chronic diseases (22,23). However, a relationship between smoking or alcohol use and colchicine adherence was not detected in the current population with FMF.

Study Limitations

A limitation of this study is the small sample size.

Conclusion

It is crucial to predict the factors affecting colchicine adherence in the management of patients with FMF. Adolescent patients, children with severe disease and frequent relapses, those treated with higher doses of colchicine, those with M694V homozygosity, and those with homozygous M694V mutations were observed to have a higher risk of colchicine non-adherence. Patients with FMF should be questioned about their medication adherence at every visit. In particular, patients with a high risk of colchicine non-adherence should be followed up more closely.

Ethics

Ethics Committee Approval: The ethics committee approval was obtained from Manisa Celal Bayar University Faculty of Medicine, Health Sciences Ethics Committee (29.12.2021-20.478.486/1117).

Informed Consent: Informed consent was taken from the participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: E.N.A.O., E.E., Ö.B., P.E., Design: E.N.A.O., Ö.B., P.E., Data Collection and/or Processing: E.N.A.O., E.E., Analysis and/or Interpretation: Ö.B., P.E., Writing: E.N.A.O., E.E.

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Case Report

Neonatal Lupus Erythematosus-Beyond Conduction Defects

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ABSTRACT

Neonatal lupus erythematosus is an uncommon disease; frequently undiagnosed, produced by the transplacental passage of autoantibodies such as anti-Ro/SSA and anti-La/SSB. Here, we discuss a case of a preterm baby with intracardiac calcification and right ventricular dysfunction detected antenatally and managed successfully with steroid and intravenous immunoglobulins.

Keywords: Lupus erythematosus, heart failure, neonatal critical care

Introduction

Neonatal lupus erythematosus (NLE) is a rare disease; frequently undiagnosed, which is caused by the transplacental passage of autoantibodies such as anti-Ro/SSA and anti-La/SSB1. NLE presents with multi-organ involvement but the skin and heart are the main targets. Mothers with anti-Ro/SSA and anti-La/SSB antibodies face a 2% risk of having a baby with myocardial calcification, cardiac dysfunction and heart blocks (1).

Case Report

A late preterm (36 weeks), appropriate for gestational age, male baby was delivered with a birth weight of 2,690 kg to a 31 year-old mother who was diagnosed as having systemic lupus erythematosus seven years prior to conception, which was confirmed by anti-Ro and anti-La antibodies. She was treated with oral prednisolone for one year initially and then started on oral hydroxychloroquine, which was continued. The initial ultrasound scan in the present pregnancy was carried out at four months of gestation and was normal. A second scan carried out at 32 weeks of gestation showed foetal cardiomegaly with pericardial effusion. Foetal echocardiography (ECHO) showed findings of a dilated right atrium (RA), right ventricle (RV) and multiple intracardiac calcifications predominantly in the right and left papillary muscles, and mild pericardial effusion with mild RV dysfunction.

In view of the foetal cardiac involvement, hydroxychloroquine was stopped and oral betamethasone was given for 2 weeks at a dose of 3 mg/day. Repeat foetal ECHO carried out at 36 weeks of gestation showed multiple intracardiac calcifications, grossly dilated RA & RV with significant RV dysfunction. Hence, the mother was advised to have an early delivery in order to avoid further complications.

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The baby was born by normal vaginal delivery and was placed in the neonatal intensive care unit due to tachypnea. ECHO carried out on day 1 of life showed a large patent ductus arteriosus (5 mm) with bidirectional shunt, dilated RA, RV with RV dysfunction and mild pericardial effusion (Figure 1). The baby was started on intravenous furosemide, dobutamine and oxygen support. Electrocardiogram (ECG) showed first degree heart block.

Initial haemoglobin, white blood cell counts and platelet counts were within normal limits. Liver enzymes were normal: Anti-Ro: >240 U/mL, anti-La: 0.7 U/mL and anti DNAse <10 IU/mL. As we noted significant cardiac lesions with ventricular dysfunction, intravenous immunoglobulin (IVIG) 1 g/kg/day was given. At 48 hours of life, the tachypnea decreased, however significant tachycardia persisted. At 72 hours of life, repeat ECHO showed patent foramen ovale with left to right shunt, dilated left atrium (LA) & left ventricle (LV) and mild RV. The LV dysfunction, LV ejection fraction was 45% with no pericardial effusion. Due to the low ejection fraction, syrup digoxin was started at a dose of 10 mcg/kg. Repeat ECHO on day 5 showed multiple intracardiac calcifications, patent foramen ovale with left to right shunt, mildly dilated LA & LV, fair LV function with good RV function. Clinically, the baby was stable and so the baby was moved to the mother's bedside on day 6 of life with oral digoxin and furosemide. On follow-up, ventricular function returned to normal by 3 months of age and the child was asymptomatic. All cardiac medications were stopped in view of this. However, the ECG was still showing a first degree heart block.

Discussion

Cardiac manifestations, being the second most common presentation in NLE, usually include conduction abnormalities and cardiomyopathy which may lead to heart failure in the new-born period (1). Cardiac damage in the form of calcification and collagen deposition secondary to existing blocks may be seen. In addition, damage to the valves and valve apparatus, which includes fibrosis and calcification of the papillary muscle, myocarditis, pericardial effusion and endocardial fibroelastosis are also known to occur (2).

Very few studies have shown findings beyond the conduction system. Cuneo et al. (3) reported two cases of atrioventricular valve insufficiency due to chordal rupture from the papillary muscles in a 34 weeks of gestation foetus and a 6-month old infant born to mothers who tested positive for anti-Ro 52 antibodies. Morais et al. (4) described a male infant born to a mother who had unexplained fever and vasculitic lesions on her extremities and face as having hyperechogenic lesions on the anterior papilar muscle of the LV and on the lateral cusp of the tricuspid valve. The occurrence of dilated cardiomyopathy has been reported to be between 5 to 28.6% in babies with NLE. The spectrum of neonatal lupus now includes many cases which have described the occurrence of endomyocardial fibroelastosis (5). Carolina Llanos et al. (6) conducted a study of 18 lupus autopsy cases. Three of these cases showed findings of papillary muscle fibrosis, microcalcification of the atrial septum, soft tissue adjacent to the atrioventricular node and ventricles, dilated atria and ventricles, valvular disease, pericardial effusion and endocardial fibroelastosis.

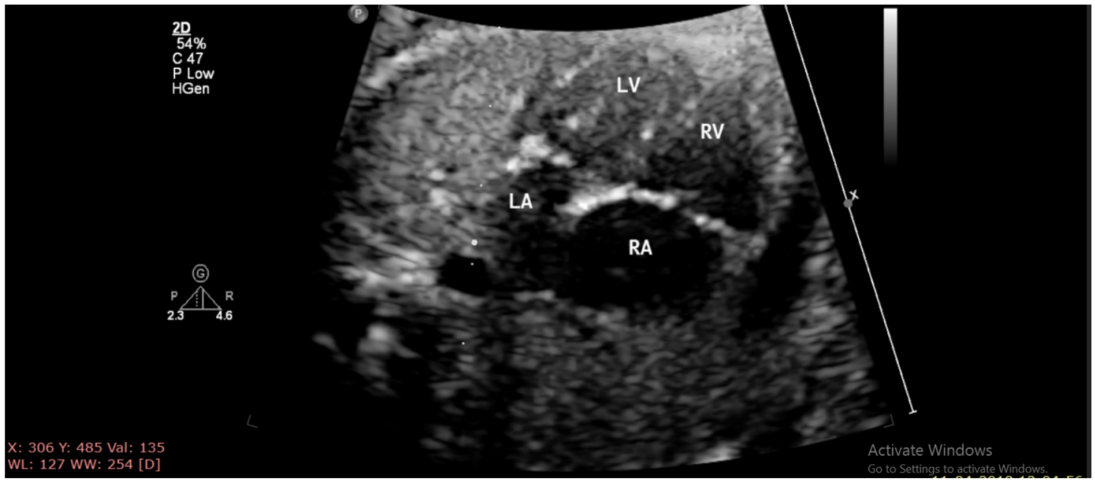

Figure 1. Echocardiogram on day 1 of life showing a 5 mm patent ductus arteriosus, dilated RA, RV with RV dysfunction and mild pericardial effusion
LA: Left atrium, LV: Left ventricle, RV: Right ventricle, RA: Right atrium

In this present case, foetal ECHO carried out at 32 weeks of gestation showed multiple intracardiac calcifications mainly in the papillary muscles with mild pericardial effusion and mild RV dysfunction. The mother was started on corticosteroids based on a recent study conducted by Buyon et al. (7) which showed that antenatal steroids help in preventing cardiac damage or its progression. Repeat ECHO at 36 weeks of gestation showed progressively dilated RA and RV, significant RV dysfunction in addition to multiple intracardiac calcifications. Post-delivery, the baby was started on inotropes and diuretics in view of the significant right ventricular dysfunction. In order to reduce further cardiac damage by transplacentally transferred maternal anti-Ro and anti-La antibodies, IVIG transfusion was given. Post IVIG infusion, an improvement in clinical status and ventricular function was noted along with resolution of the pericardial effusion. The use of IVIG has been studied alone or along with dexamethasone or plasmapheresis (8). Trucco et al. (9) observed improvement in ventricular systolic function in eleven neonates who received IVIG within the first few days with or without steroids. IVIG therapy is more beneficial if it is given early in the pregnancy. More importantly, waiting to provide IVIG until after birth may eliminate the added benefits of reducing maternal antibody exposure and myocardial damage in utero. However, a study by Alsaleem. (8) showed antenatal use of low dose IVIG at 400 mg/kg did not prevent the recurrence of heart block in a series of babies. More studies and data are needed to understand the spectrum of cardiac involvement in terms of ventricular dysfunction, multiple calcifications other than heart blocks and the role of IVIG in post-natal life.

Babies with lupus erythematosus need regular follow-up. Maternal anti-Ro/La antibodies usually disappear by 6 months of life. These babies can develop bradycardia, prolonged page rank interval, cardiomyopathy and/or heart block so serial monitoring by ECG and ECHO is necessary (1). NLE with cardiac involvement is associated with 20-30% mortality in neonatal life. In 10% of cases, transient ECG alterations were found during follow-up. Persistent anti-Ro/La antibodies warrant follow-up until adulthood. Additionally, the rate of subsequent pregnancies being affected is 12-25% (10).

Conclusion

NLE with cardiac involvement is a serious condition and therapy should either be targeted to eliminate the necessary factor (no antibody, no disease) or to modify the inflammatory component before it provokes irreversible cardiac damage. Combined steroid and IVIG therapy shows promising benefits.

Ethics

Informed Consent: Informed consent was taken prior to writing this case report from the patient's parents.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: P.A., A.S., Design: S.K., A.S., A.R., Data Collection or Processing: P.A., S.K., Literature Search: P.A., A.R., Writing: P.A., S.K., A.R.

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