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PRISMA statement of preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/);

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Conclusion: Should summarize the results of the study, the clinical applicability of the results should be defined, and the favorable and unfavorable aspects should be declared.

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Editorial

Dear Readers,

We are happy to welcome you to the last issue of The Journal of Pediatric Research in 2019.

In this issue, 15 articles worth reading from different pediatric disciplines including 12 original research papers and 3 case reports are presented.

I would like to acknowledge the members of our editorial board, reviewers, authors and Galenos Publishing House for preparing the fourth issue of 2019.

Special thanks to our esteemed Turkish engraving artist Rüveyda Koyuncu Colombin for sharing her meaningful work titled "L'Arbre de la Vie" on the cover of this issue.

In 2020, we will continue to work with all our efforts to achieve our goals and to offer you a highly qualified pediatric journal.

We look forward to seeing your scientific research articles in our future issues.

Best wishes and a happy new year.

December 2019

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Original Article

Effects of Chronic Gastritis on Sleep and Quality of Life in Adolescents

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ABSTRACT

Aim: This study aims to evaluate the sleep quality and the quality of life (QoL) of adolescents with chronic gastritis, and determine the related factors.

Materials and Methods: This study included patients who were diagnosed with chronic gastritis both clinically and histopathologically. The Pittsburgh Sleep Quality Index and Epworth Sleepiness scale were used to assess sleep quality, and the Pediatric Quality of Life Inventory was used to assess QoL. The control group included healthy volunteers with no chronic diseases and no gastrointestinal system complaints.

Results: Fifty-six patients with gastritis and 55 healthy volunteers were included. The patients with gastritis were found to have significantly lower overall QoL subscale, and total scale scores, except for the social functioning total score. Except for the subjective sleep quality, significant differences were seen between the groups in the sleep quality subscale, total scale, and sleepiness scale averages. The total score of the sleep quality scale was significantly higher in patients who had lower incomes than expenditure. There were no significant differences between the obese or overweight patients with gastritis and the rest of the gastritis patients in the study sample. There were no significant differences found between the *Helicobacter pylori* positive and negative gastritis patients in terms of the total QoL and sleepiness scale scores.

Conclusion: This study is important because it is the first study in adolescents in this respect. The sleep and QoL scores of those adolescents with chronic gastritis were lower than the control group.

Keywords: Gastritis, quality of life, sleep, adolescent

Introduction

Gastritis is defined as the inflammation of gastric mucosa with microscopic evidence (1). Gastritis and peptic ulcer disease are the results of an imbalance between the mucosal defensive and aggressive factors. Gastritis and peptic ulcer disease can be divided into two major categories: namely primary and secondary (such as hypersecretory conditions, stress, granulomatous and immunologic/allergy situations) on the basis of the underlying etiology (2). Most cases of primary or unexplained gastritis are now known to be caused by *Helicobacter pylori (H.pylori)* (3). Data on acid secretion in children are limited and not up to date and their interpretations complicated by the considerable overlap in acid secretion between children with and without ulcers

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(4). There are no accurate figures related to the precise incidence of gastritis in children. As for ulcer disease, *H. pylori* is probably no longer the major cause of gastritis in many parts of the world (5). In a prospective study of 100 children who underwent upper gastrointestinal system (GIS) endoscopy due to dyspeptic symptoms, 79% were found to have gastritis (none had ulcer disease), of whom only 33% had *H. pylori* infection (6).

The Sydney classification of gastritis aims to combine topographic, morphologic, and etiologic information to form a clinically relevant scheme (7). This classification and grading, which now incorporates the use of a visual analogue scale, is accepted as the standard research method by which all gastric biopsies from adult patients are commonly assessed (8). The updated Sydney system is currently the most widely accepted classification for gastritis, even in children (8).

In gastritis cases, the etiological factors and the patient's response to the inflammation may change the clinical findings. Inflammation of the gastric mucosa is among the most frequent causes of abdominal pain in children (9). Gastritis can affect an individual's daily activities, and this creates an important health problem from both the social and economic points of view. Gastritis may lead to an observable worsening in the quality of life (QoL) and affect the quality of sleep for adult patients (10,11). There are no studies in the contemporary international literature that are focused on the quality of sleep and life in children and adolescents with gastritis. Therefore, this study aimed to conduct an evaluation of the sleep quality and life quality of children and adolescents with gastritis and identify the relevant factors.

Materials and Methods

Study Population

This study included patients between the ages of 13 and 18 years old who applied to İzmir Tepecik Training and Research Hospital Pediatric Gastroenterology Clinic between August 2017 and October 2017 and received clinical and histopathological chronic gastritis diagnoses. These patients underwent upper GIS endoscopies; gastric biopsy samples were taken from the antrum and corpus due to gastrointestinal symptoms (such as chronic abdominal pain, dyspepsia, vomiting, and abdominal distention) that had been ongoing for at least one month (8). Patients diagnosed with a disease other than gastritis via clinical, endoscopic, and histopathologic findings (such as eosinophilic esophagitis, reflux esophagitis, or inflammatory bowel disease) were not included in this study. In the literature, it has been shown that children may experience impaired QoL and sleep in different chronic diseases (12-14). For this reason, gastritis patients with additional chronic diseases were excluded from this study. Upper gastrointestinal endoscopy biopsies were assessed according to the Sydney classification by a pathologist. Those adolescents who were found to have chronic gastritis, with no additional chronic disease and additional histopathologic findings in the pathology reports and who agreed to participate in the study were included. The Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness scale (ESS) were used to evaluate sleep quality. QoL was evaluated via the Pediatric Quality of Life Inventory (PedsQL), which is suitable for this age group. Only those children who could read, understand, and complete all of the scales used were included in this study.

The data obtained was assessed via comparisons with a healthy control group. Healthy controls were selected from healthy volunteers who presented to the pediatric gastroenterology and pediatric outpatient clinics. For the comparisons, the sleep and life quality scales were applied to a group of healthy volunteers of the same age and gender who did not have any chronic diseases or GIS complaints. The patients' demographic findings, complaints during application, endoscopic findings, and *H. pylori* positivity status were identified and evaluated together with the life and sleep qualities. In addition, the relationship between the income levels of the patients and sleep quality was assessed. For this purpose, patients were divided into three groups as follows; patients whose income is lower than their expenditure, patients whose income is equal to their expenditure, and those patients whose income is higher than their expenditure, the patients were asked to state their income status accordingly. Each patient's body mass index (BMI) percentile was determined according to their age and sex, and those with BMI ≥95 percentile were considered as obese, while those with a BMI between the 85th and 95th percentile were classified as overweight (15). In addition, the relationship between BMI and the life and sleep qualities were assessed. Healthy volunteers with normal BMI ratios that ranged between the 5th and 95th percentiles were included in the control group. Children who were not in the 5 to 95 percentile range were not included in the control group. Neither the patient nor control groups had any drug use or acid suppressive treatment history and did not have any diseases that could affect sleep quality, such as sleep apnea.

The study was approved by the University of Health Sciences, İzmir Tepecik Training and Research Hospital Ethics Committee (approvel number: 17.08.2017/18). Consent form was filled out by all participants.

Study Scales

Pediatric Quality of Life Inventory

The PedsQL was developed for children, and it is a widely used, straight forward, and generic QoL measure that can be implemented in a short time period (16). There are two different scale forms, a self-reported scale and a parent-reported scale. Each scale is modified according to the following age groups; 2-4, 5-7, 8-12, and 13-18 years-old and the modifications were designed by accounting for the characteristics of each age group. The scale consists of four subgroups that aim to question physical, emotional, social, and school related functions. The self-reported and parent-reported forms each consist of 23 items. The score of these items is linearly converted to a value between 0 and 100, and a higher number of points indicate a higher QoL. A Turkish validity and reliability study of the PedsQL has been conducted for adolescents (17).

Pittsburgh Sleep Quality Index

The PSQI is a self-reported scale consisting of 19 items that evaluate sleep quality and sleep disorders over the last month. Each component is scored between 0 and 3 points, and a total of 7 components (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, daytime dysfunction) give the total score of the scale. A total point score of over 5 indicates "bad sleep quality" (18). The Turkish version of the PSQI was developed by Agargun et al. (19).

Epworth Sleepiness Scale

The ESS is an 8-item self-administered scale that is easy to use. It evaluates the general sleepiness of an individual in 8 different daily life situations. The ESS score ranges between 0 to 24 and a higher ESS score indicates greater daytime sleepiness (20). The ESS has a high sensitivity and a high specificity with a cut-off score of more than 10 indicating an abnormal level of daytime sleepiness (21). The Turkish validity and reliability study of the ESS was conducted by Izci et al. (22).

Statistical Analysis

The quantitative variables are expressed as the mean and standard deviation, while the categorical variables are expressed as numbers and percentages. The conformity assessment of the normal distribution of the numerical data for a single sample was performed using the Shapiro-Wilk test. Bivariate comparisons were conducted with chi-square test (with Yates' and Fisher's corrections when needed), and for the independent groups, Student's t-test or Mann-Whitney U test was used depending on the distribution. Bivariate correlations were conducted with Pearson's or Spearman's correlation analyses depending on the normal distribution. All of the statistical tests were performed with the Statistical Package for the Social Sciences version 18.0 (SPSS, Inc., Chicago, IL, USA). A p value of less than 0.05 was considered as statistically significant.

Results

This study focused on 56 patients with chronic gastritis and 55 healthy volunteers. The age and gender distributions of the patient and control groups were similar (Table I). At the time of presentation to the hospital, 60.7% of the patients with gastritis presented with complaints of dyspepsia, 30.4% had abdominal pain, 30.4% had vomiting, 17.9% had nausea, and 10.7% presented with complaints of abdominal distention. Endoscopic assessment revealed that 34 patients (60.7%) had pangastritis and 22 patients (39.3%) had antral gastritis. There was no statistical difference between the complaints of those children who had pangastritis and those children who had antral gastritis according to the chi-square analysis (p=0.758, z=6.548). Also, three patients had bulbus ulcers and one patient had an antral ulcer. Similarly, no statistically significant difference was found between the complaints of adolescents with or without ulcer (p=0.909 z=0.958). The upper GIS

Table I. Socio-demographic data of the patients and controls

	Patients	Controls	p value
Age (mean years ± SD)	15.48±1.61	14.94±1.79	0.101
Gender			
Girls (n, %)	34 (60.7%)	28 (50.9%)	0.253
Boys (n, %)	22 (39.3%)	27 (49.1%)	
Body mass index percentile (mean ± SD)	38.7±36.5	54.5±26.2	0.01
Economic condition			
Less income than expenditure (n, %)	24 (42.9%)	16 (29.1%)	0.74
Equivalent income and expenditure (n, %)	19 (33.9%)	16 (29.1%)	
More income than expenditure (n, %)	13 (23.2%)	23 (41.8%)	

SD: Standard deviation

endoscopy biopsy samples of the patients were evaluated histopathologically, and it was determined that 48 (85.7%) of the patients had non-atrophic pangastritis, 6 (10.7%) had antral predominant non-atrophic gastritis, and 2 (3.6%) had atrophic pangastritis.

It was determined that those patients with gastritis had lower scores than the healthy controls, which was statistically significant in all the QoL subscale scores and in the total scale score, with the exception of the social functioning total score (Table II). A comparison of the sleep quality of the gastritis patients with that of the healthy control group showed that there was a statistically significant difference between the two groups in all the subscale scores and the total scale score averages, except for subjective sleep quality (Table III). There was no statistically significant relationship between sleep quality and symptoms (r=-0.069, p=0.612). Moreover, the average sleepiness scale score of the gastritis patients was significantly higher than the average of the healthy controls (Table III). A comparison between the female and male patients suggested that there was not a statistically significant difference between the genders regarding their QoL, sleep quality, and sleepiness total scale scores (p=0.27, p=0.07, and p=0.6, respectively).

There was no significant difference between the patient and the control groups regarding their income and expenditure (Table I). Also, no statistically significant difference was found between the groups according to their economic conditions concerning the average of the life quality subscale and total scale scores and the sleepiness scale score. In the patient group, the sleep quality scale total score of those with lower incomes than expenditures was meaningfully higher when compared to those whose incomes were either equal to or higher than their expenditures (p=0.024); while there was no significant difference between the sleep quality of the control group and economic conditions (p=0.958). According to the Spearman correlation analysis, there was no correlation between sleep quality and socio-economic status (r=-0.096, p=0.482).

Eleven (19.6%) of the patients with gastritis were considered to be obese or overweight. Comparisons of these patients with the other gastritis patients showed that there was no statistically significant difference regarding the QoL, sleep quality total scale score, and sleepiness scale average score (p=0.28, p=0.17, and p=0.63, respectively).

H. pylori was detected in 25 (44.6%) of those patients who were confirmed to have gastritis via histopathology. The comparison of *H. pylori* positive patients with the *H. pylori* negative patients showed that there was no statistically significant difference between these two groups concerning the QoL and sleepiness scale total scores (p=0.89 and p=0.38, respectively). The assessment of the two groups concerning sleep quality showed that there was a statistically significant difference in the sleep duration subscale score (p=0.029), but not in the other subscales and total scale scores (p=0.96).

Table II. Assessment of the quality of life of the gastritis patients and the healthy controls

	Patients	Controls	p value*
Pediatric Quality of Life Inventory			
Physical health total score (mean ± SD)	74.1±15.65	94±4.97	<0.001
Emotional functioning total score (mean ± SD)	64.82±19.9	86.81±9.54	<0.001
Social functioning total score (mean ± SD)	90±12.48	90.81±7.97	0.715
School functioning total score (mean ± SD)	62.41±20.71	84.90±9.35	<0.001
Total score (mean ± SD)	72.34±15.51	87.43±6.43	<0.001

*Student's t-test was applied
SD: Standard deviation

Table III. Assessment of the Pittsburgh Sleep Quality Index and Epworth Sleepiness scale results

	Patients	Controls	p value**
Pittsburgh Sleep Quality Index			
Subjective sleep quality (mean ± SD)	0.09±0.39	0.12±0.33	0.58
Sleep latency (mean ± SD)	2.43±1.89	0.46±0.64	<0.001
Sleep duration (mean ± SD)	0.50±0.68	0.05±0.23	0.013
Habitual sleep efficiency (mean ± SD)	0.85±0.77	0.56±0.71	0.04
Sleep disturbances (mean ± SD)	1.14±0.48	0.80±0.40	<0.001
Use of sleeping medication (mean ± SD)	0.69±1.04	0.07±0.26	<0.001
Daytime dysfunction (mean ± SD)	2.17±1.40	0.21±0.45	<0.001
Total score (mean ± SD)	7.7±3.14	2.5±1.5	<0.001
Epworth Sleepiness Scale			
Total score (daytime sleepiness) (mean ± SD)	4.01±2.34	2.81±1.18	0.001

**Student's t-test was applied
SD: Standard deviation

Discussion

Children with functional gastrointestinal disorders, such as functional abdominal pain, functional dyspepsia, and irritable bowel disease, have been reported to have significantly lower life quality than healthy controls (12). Several studies point out a deterioration in the QoL linked with chronic gastrointestinal diseases such as gastroesophageal reflux, constipation, and inflammatory bowel disease during childhood (12,13,23). It has also been reported that the low QoL of children with constipation improved after they received constipation treatment (24). In another study conducted on dyspeptic pediatric patients who had esophagitis or normal histological findings, after an average of 7.6 years of follow up, it was found that during their adolescence and young adulthood period, these patients had lower QoL scores, worse dyspeptic symptoms, and more functional insufficiency when compared to a control group (25). Nevertheless, there are no studies in the literature considering life and sleep qualities together in adolescents who have gastritis.

Studies conducted on adults with gastrointestinal diseases, such as peptic ulcers and gastroesophageal reflux, have reported lower life quality scores than the normal population, but also found significantly increased life quality scores after the treatment (26,27). A study on adults showed that patients with chronic gastritis had lower average scores when compared to those patients with peptic ulcers in all the life quality subscales, except for the physical functioning scale score (10). When compared with the normal population, both groups of patients had lower qualities of life scores (10). In our study, we examined the effects of gastritis on the life and sleep qualities of adolescents, and observed that those adolescents with gastritis had lower life qualities in all subscales, except for the social functioning scale score and the total score. A previous study from China that focused on adult patients with gastritis and peptic ulcers indicated that women with low-income levels had a lower QoL. The differences in the distribution of the women and men in both the patient groups were reported to affect these results (10). In our study, the QoL assessment of those patients with gastritis related to their gender and income level did not reveal a statistically significant difference.

Sleep is a fundamental and essential daily life activity that affects the life quality and health of human beings (28). Sleep quality can be affected by many factors, such as lifestyle, environmental factors, work, social life, economic conditions, general health state, and stress (29,30). In our study, while sleep quality was poor in chronic gastritis patients whose expenditure was higher than their incomes, in the control group, income level had no adverse effect on sleep quality. However, the limitation of this study is that our patients were not assessed for negative factors such as a negative social environment or unhealthy living conditions (access to clean water and food, a non-hygienic living space or their nutrition characteristics). In our study, it is seen that the gastritis patients had worse sleep quality scores than the controls regarding all the subscale scores and the average of the total scale scores, except for the subjective sleep quality score. Subjective sleep quality is a component that is based on someone's interpretation of what they think about their sleep quality. The fact that our patients are not significantly different from the controls regarding subjective sleep quality may be related to their inability to interpret sleep qualities as poor or to be unaware of their sleep quality. Daytime sleepiness is an important clinical and public health problem that reduces the QoL significantly. In our study, we determined that the gastritis patients have significantly higher daytime sleepiness scale scores than the healthy controls. We think that various symptoms related to gastritis, such as abdominal pain, dyspepsia and vomiting affect the daily functioning of the individual and their daytime sleep pattern. However, in our study, when the sleep quality and the symptoms were examined, a statistically significant relationship was not found. In our study, the comparison between the male and female patients regarding their sleep quality and daytime sleepiness revealed that there was no statistically significant difference between the genders. Moreover, the detection of *H. pylori* in the gastritis patients did not have any effects on the QoL, daytime sleepiness, or general sleep quality, but the sleep duration was shorter when compared to the *H. pylori* negative patients.

A study conducted by Filik and Ozer (11) reported a significant relationship between gastritis or erosive esophagitis and short sleep duration in adults. This relationship was especially meaningfully higher in overweight or obese patients. It has been reported that a high BMI can lead to sleep disorders in adults and that obese patients may suffer from sleep disorders and sleeping difficulties (31,32). Moreover, childhood obesity may lead to many complications that can damage QoL, such as poor academic performance, psychological findings, lifelong obesity, and cardiovascular disease (33). In one study of 144 obese and overweight children, sleep quality scores assessed via the

PSQI and were found to be worse than those of healthy children (34). In our study, 19.6% of those patients with gastritis were obese or overweight, and their sleep qualities and qualities of life were not worse when compared to the rest of the gastritis patients in the study sample.

Conclusions

This study is important because it is the first to evaluate the QoL and sleep quality in adolescents with chronic gastritis. In our study, adolescents with chronic gastritis had poor sleep quality and lower QoL scores. The limitations of this study are the small sample size and the unevaluated negative factors such as negative social environment and unhealthy living conditions. In addition, we were not able to assess the sleep and QoL of our patients after receiving gastritis treatment. For this reason, we think that future studies evaluating chronic gastritis adolescents will be useful.

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Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences, Tepecik Training and Research Hospital Ethics Committee (approvel number: 17.08.2017/18).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Medical Practices: Y.Ç.A., G.Ö., M.K., Concept: Y.Ç.A., G.Ö., M.K., Design: Y.Ç.A., G.Ö., M.B., Data Collection or Processing: Y.Ç.A., G.Ö., M.K., Analysis or Interpretation: Y.Ç.A., G.Ö., M.B., Literature Search: Y.Ç.A., G.Ö., M.K., Writing: Y.Ç.A., G.Ö.

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Original Article

Determination of Perceived Social Support and Burnout Levels of Mothers of Children with Intellectual Disability

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ABSTRACT

Aim: The aim of this study is to determine the correlation between the perceived social support and burnout levels of the mothers of intellectually disabled (ID) children and the affecting factors.

Materials and Methods: This descriptive and cross-sectional study was conducted in the fourteen Special Training and Rehabilitation Centers in the city center of Trabzon between 1st June 2014 and 30th November 2014. The sample of the study consisted of 128 mothers who had 6-14 year old children with intellectual disability. The data of the study were collected using the Personal Information Form, Maslach Burnout Inventory, and Multidimensional Scale of Perceived Social Support.

Results: In this study, more than half of the mothers were determined to have difficulty in the care of their ID children. These mothers were found to have difficulty mostly because of financial problems and their children's aggressive behavior. It was determined that the relationships of one third of these mothers with their husbands and one fourth with their healthy children and relatives were negatively affected. The burnout levels of these mothers who had difficulty in the care of their ID children, were secondary school graduate, had an extended family, were unemployed, were on social security, and an ID boy, were found to be higher. In this study, while higher Multidimensional Scale of Perceived Social Support scores of the mothers were good it was unwanted stiuation their burnout levels were above the mean.

Conclusion: It is recommended to determine multiple factors causing burnout in the mothers of ID children, accordingly to support mothers using a multi-factorial team approach through different studies to be conducted concerning this matter, and for mothers to take short vacations and participate in activities they like.

Keywords: Burnout, child, intellectually disabled, mother, social support

Introduction

According to data from the World Health Organization, it is estimated that 10% of the total population in developed countries and 13% of the total population in developing counties consist of intellectually, physically, or emotionally disabled people. A disabled child or adult is found in one of every 7-8 families (1). The ratio of disabled children in Turkey is 12.3% (2).

When a child has a disability, all members of the family are affected to various degrees. The major caregiving responsibility usually falls to the mother (2-4). Mothers

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may experience intense stress due to these responsibilities, which can lead to burnout in them (4-7). Therefore, the causes of burnout experienced especially by mothers are important. Social support behaviors such as reducing the negative outcomes of the crisis experienced by families because they have a disabled child, making them feel valuable, and love will make adaptation of these families to this process easier and will help these families emotionally and physically (2,8,9).

Social support patterns for families with a disabled child are divided into two categories, namely, formal and informal. While formal social support systems are perceived as being given by professionals, informal support systems are perceived as being given by family members, friends and being a member of social groups that are integrated into the family's daily life. Informal support is more efficient than formal support for protection against the negative effects of stress (3,9).

One of the most important factors making it easier to successfully adapt to the presence of a disabled child is to provide support services that will both help to meet the needs of the child and the family and make it easier to reduce disability-related problems (10). Unfortunately, since fathers consider their children's disease or disability to be the fault of the woman in Turkey, they refuse to give their support to their wives and the woman's immediate surroundings do not provide the required support in the period when the woman needs it most with the concern that responsibility for care of a disabled child would be left to them, and these are quite overwhelming for the woman and result in burnout. Therefore, various support systems especially for mothers with intellectually disabled (ID) children to cope with high levels of stress occurring due to the difficulties they experience and comprehensive studies to raise awareness about this issue are needed.

The aim of this study is to determine the correlation between perceived social support and burnout levels of those mothers with ID children and to detect whether or not perceived social support and burnout levels of mothers differ depending on socio-demographic variables, difficulties experienced by mothers, and the state of their personal relationships.

Materials and Methods

This is a descriptive and cross-sectional study. The study was conducted in the fourteen Special Education and Rehabilitation Centers in the city center of Trabzon between 1st June 2014 and 30th November 2014.

Ethics approval was received from Karadeniz Technical University Faculty of Medicine Scientific Research Ethics Committee (approval number: 24237859-179, date: 03.21.2014), a written permission from The Rehabilitation Centers in the city of Trabzon, and verbal consent from the participants were received. The principle of "Informed Consent" was fulfilled by informing mothers about purpose of the study, the principle of "Respect for Autonomy" was fulfilled by voluntary participation in the study and the principle of "Confidentiality and the Protection of Confidentiality" was fulfilled by saying that information to be obtained would be kept confidential.

Population and Sample Group

The population of the study consisted of the mothers of 220 ID children who were receiving regular physiotherapy and rehabilitation in special education and rehabilitation centers between the specified dates. The sample of the study consisted of 128 mothers who met the inclusion criteria and agreed to participate in the study. Children with ID, aged between 6-14 years, and informed consent of the legal primary caregiver of the child were the inclusion criteria. Families who refused to participate in the study, primary caregivers with cooperation problems and those who could not speak Turkish, and children having other disability problems (orthopedic, hyperactivity, or autism) were excluded from the study.

Materials

The data were collected using the Personal Information Form, Maslach Burnout Inventory (MBI) and Multidimensional Scale of Perceived Social Support (MSPSS).

Personal Information Form: The personal information form consists of 22 questions including the socio-demographic characteristics of the ID children and their mothers as well as their effects on their lives.

Maslach Burnout Inventory: The Maslach Burnout Inventory developed by Maslach et al. (11,12) is by far the most popular instrument to assess burnout. The validated 22-item MBI was used to assess burnout because of its proven reliability, ease of completion, validity, and applicability to the general population. The MBI identifies the frequency (how often) various feelings occur over a 12-month period, with a total of 22 questions grouped into the three dimensions, namely emotional exhaustion (EE) (EE; items 1, 2, 3, 6, 8, 13, 14, 16, and 20), depersonalization (DP) (DP; items 5, 10, 11, 15, and 22), and reduced personal accomplishment (PA) (PA; items 4, 7, 9, 12, 17, 18, 19, and

21). The answer to each question rated the experiences on a 5-point Likert scale, ranging from "never" to "everyday" (13). High scores on emotional exhaustion and depersonalization and low scores on personal accomplishment are signs of burnout.

MBI had been translated into Turkish and used as a data collection instrument in the field of medicine before (14,15). It was found to be reliable and valid. Ergin (15) found reliability coefficients to be 0.83 for EE, 0.65 for DP, and 0.72 for PA. Cronbach's alpha coefficient of the scale was determined to be 0.77. Cronbach's alpha coefficient was 0.78 for the EE subscale, 0.66 for the DP subscale, and 0.67 for the PA subscale.

Multidimensional Scale of Perceived Social Support: The MSPSS total score was used in this study. The MSPSS is a self-rating tool of perceived social support consisting of 12 questions rated on a 7-point scale developed by Zimet et al. (16). Questions are divided into 3 groups: family, friends and significant other. The 7-point scale ranges from 1 "very strongly disagree" to 7 "very strongly agree". The total scale score was used in this study, which was obtained by finding the arithmetic mean of the sum of the scores on all the items. A high score indicates a high level of perceived social support. The items in the MSPSS have excellent internal consistency (Cronbach's alpha=0.84-0.92) and strong test-retest reliability (r=0.72-0.85) (17). Total and subscale scores are generated. Higher scores indicate better support. Internal consistency (0.90-0.95) and validity are excellent.

The lowest score to be obtained from the scale is 12, the highest score is 84. A validity and reliability study of the scale was conducted by Eker and Arkar (18) in Turkey. Cronbach's alpha coefficient was 0.89 for the scale, 0.85 for the family subscale, 0.88 for the friend subscale, and 0.92 for the significant other subscale (19). In this study, it was determined that Cronbach's alpha reliability was 0.88 for the scale, 0.81 for the significant other subscale, 0.82 for the family subscale, and 0.89 for the friend subscale.

Data Collection

The data were collected by researchers using the face-to-face interview method. It took on average 30-35 minutes to collect the data. The instruments were tested in a pilot study that included 10 mothers, and confirmed a high level of item acceptance and comprehension. The assessments were conducted by the children's own physiotherapists, who had at least 5 years of experience in treating disabled children.

Statistical Analysis

The SPSS 19.0 package software was used to analyze the data of the study. The data were assessed by using the Cronbach's alpha coefficient, percentage distribution, mean, standard deviation, Pearson's correlation analysis, independent samples t-test, one way analysis of variance (ANOVA) and the Tukey test as an advanced analysis for values determined to be significant in the analysis of variance. The confidence interval was 95%; $p<0.05$ was considered to be statistically significant.

Results

The Socio-demographic Characteristics of Participants

It was determined that 40.6% of the mothers were 40 years old or older, 65.6% were primary school graduates, 7% were employed, 85.9% had a nuclear family, 18.8% had 4 or more children, and 32.8% had kinship with their spouses. The average age of the disabled children included in the study was 11.30±3.88 years and 58.6% were male (Table I).

Comparison of the Mothers' Characteristics and the Multidimensional Scale of Perceived Social Support

In the study, it was found that the mothers' mean scores were 58.22±19.46 from MSPSS, 19.92±7.97 from the significant other subscale, 19.97±7.80 from the family subscale, and 18.32±8.58 from the friend subscale.

MSPSS mean scores of mothers aged between 20-30 years were 62.04±14.45. There was a statistically significant difference between mother's age and the family subscale's mean score. The MSPSS mean scores (59.55±18.98) of married women were higher than single women and the difference between marital status and MSPSS/subcales (significant other and friend subscales) was statistically significant. In the study, the subscales' mean scores of those mothers who had an extended family type were higher than the others and the difference between family type and the significant other subscale was statistically significant. MSPSS and its subscales' mean scores of those women who had no kinship with their spouses were higher and the difference between them was statistically significant (Table I).

In the study, the percentage of mothers who have difficulty in the care of their ID children was 61.7%. These mothers experienced financial problems, moral depression, and difficulty due to the extremely angry and aggressive behaviors of their disabled child. In the study, the percentage of mothers whose relationships with their husband was

negatively affected was 22.7%, with their healthy children, the percentage was 19.5%, and with their relatives, it was 17.2% (Table II).

It was found that there was a statistically significant difference between mothers who have difficulty in their child's care, have financial difficulty and mean scores of the friend subscale. There was a statistically significant difference between mothers affected relationship with relatives, receiving support in care and mean scores of the family subscale ($p<0.05$, Table II).

Comparison of the Mothers' Characteristics and the Maslach Burnout Inventory

The total mean scores of MBI were 29.11±12.14. It was found that the EE subscale's mean score was 14.83±7.78, the DP subscale's mean score was 4.94±4.03, and the PA subscale's mean score was 9.33±5.60.

In this study, there was found to be a statistically significant negative correlation between the family's income level and the mean scores of the DP subscale. It was determined that there was no significant correlation between the age of the ID children and the mean scores of the MBI (Table III).

In this study, the MBI's mean scores of those mothers aged between 20-30 years and over 40 years were 29.23±10.82 and 29.82±12.26, respectively. Those mothers who had graduated from a university had lower scores for the MBI and its subscales. It was determined that the difference between mothers' socio-demographic characteristics and the mean scores of the MBI was not statistically significant (Table III).

The MBI's mean scores (30.53±12.27) of those mothers who had difficulty in the care of their child were higher. In this study, the difference between those mothers who had difficulty in the care of their children and the mean scores of the EE and DP subscales were statistically significant ($p<0.05$, Table IV).

It was determined that those mothers who stated the status of their relationship as "no knowledge about their spouse", were 13.14±6.51 of the PA subscale's mean scores and the difference between them was statistically significant. The EE and DP subscales' mean scores of those mothers with financial difficulties were 20.27±8.62 and 7.63±4.24, respectively. Those mothers supported by their surrounding (neighbors, relatives), it was 19.80±13.47 for the mean score of the PA subscale and the difference between them was statistically significant.

Correlation Between Multidimensional Scale of Perceived Social Support and Maslach Burnout Inventory

In this study, there was a negative significant correlation ($r=-0.216$, $p=0.014$) between the mean scores of the family subscale and the mean scores from the PA subscale. It was determined that there was also a negative significant correlation among the mean scores of the friend subscale and the mean scores of the MBI and its EE and DP subscales (respectively, EE: $r=-0.178$, $p=0.044$; DP: $r=-0.180$, $p=0.042$; MBI: $r=-0.192$; $p=0.030$), (Table V).

Discussion

Comparison of Some of the Mothers' Characteristics and the Multidimensional Scale of Perceived Social Support

It was found that there was a positive significant correlation among family's income level and the mean scores of the MSPSS, significant other and friend subscales. Gölamış (20) found that the mothers' perceived social support levels differed according to level of income. Erhan (21) stated that mothers received lower social support as their income level decreased. The results of this study were found to be similar to those results of the previous studies.

Those mothers aged between 20-30 years had higher mean scores on the family subscale. There was a statistically significant difference between the mother's age and the mean scores of the family subscale. This result can be explained by the fact that young mothers are supported by their families more until they get used to this situation and learn how to cope with the problem.

It was seen that married mothers had higher means scores on the MSPSS, significant other and friend subscales. It can be asserted that mothers receive more social support because marriage is an entity accepted by the family and social surrounding due to the structure of Turkish society. It was thought that the low number of single mothers compared to married ones was also effective in this result. In contrast to the results of this study; Hartley and Schultz (22) reported that mothers displayed more symptoms of stress and depression compared to fathers amongst the married couples and accordingly mothers had more unmet social support needs.

In this study, those mothers who had an extended family type had higher mean scores on the MSPSS, and its subscales. There was a statistically significant difference between family type and mean scores on the significant other subscale. This case can be explained by the fact that the mother received more support for household chores,

Table I. Comparison of the mothers' socio-demographic characteristics and MSPSS scores

		MSPSS							
		Significant other		Family		Friend		Total	
	Mean ± SD	Mean ± SD	Test and sig.	Mean ± SD	Test and sig.	Mean ± SD	Test and sig.	Mean ± SD	Test and sig.
Child's age	11.30±3.88	-	r=-0.057 p=0.520	-	r=0.028 p=0.751	-	r=-0.109 p=0.221	-	r=-0.060 p=0.500
Family's income level (TL)	761.23±524.66	-	**r=0.203 p=0.021**	-	r=0.128 p=0.150	-	**r=0.212 p:0.016**	-	**r=0.228 p=0.010**
	n (%)								
Mother's age									
20-30 years	21 (16.4)	21.52±7.41	F=1.647 p=0.197	21.52±8.51	**F=3.266 p=0.041**	19.00±6.64	F=0.185 p=0.831	62.04±14.45	F=1.382 p=0.255
30-40 years	55 (43.0)	18.49±8.56		17.98±8.07		18.56±8.53		55.03±19.82	
40 ↑ years	52 (40.6)	20.80±7.41		21.46±7.27		17.78±9.40		60.05±20.61	
Marital Status									
Married	121 (94.5)	20.62±7.55	**t=4.410 p=0.000**	20.02±7.84	t=0.290 p=0.772	18.90±8.32	**t=3.304 p=0.001**	59.55±18.98	**t=3.332 p=0.001**
Single	7 (5.5)	7.85±4.84		19.14±7.58		8.28±7.04		35.28±12.84	
Educational level									
Illiterate	15 (11.7)	15.13±6.99	F=2.246 p=0.068	18.33±6.45	F=0.668 p=0.615	16.66±8.71	F=0.883 p=0.477	50.13±14.64	F=1.493 p=0.208
Primary school	84 (65.6)	20.69±8.12		19.94±8.21		18.44±8.69		59.07±19.93	
Secondary school	11 (8.6)	20.45±8.00		22.36±6.48		17.27±8.48		60.09±21.24	
High school	14 (10.9)	18.50±7.12		19.07±8.41		18.14±8.71		55.71±20.21	
University	4 (3.1)	25.50±4.35		23.50±3.31		25.50±3.78		74.50±4.93	
Family type									
Nuclear	110 (85.99	19.87±7.87	**F=6.274 p=0.003**	19.80±7.57	F=0.918 p=0.402	18.37±8.45	F=0.543 p=0.582	58.05±19.17	F=2.834 p=0.063
Extended	15 (11.7)	23.13±6.23		22.00±8.96		18.93±9.66		64.06±19.27	
Broken	3 (2.3)	6.00±3.46		16.00±10.81		13.33±9.01		35.33±19.55	
Employment status									
Yes	9 (07.0)	21.77±8.012	t=0.720 p=0.473	21.11±6.43	t=0.451 p=0.653	20.77±8.82	t=0.890 p=0.375	63.66±20.23	t=0.869 p:0.387
No	119 (93.0)	19.78±7.98		19.89±7.91		18.13±8.57		57.81±19.43	
Social security									
Yes	101 (78.9)	20.21±7.95	t=0.790 p=0.431	20.26±7.92	t=0.814 p=0.417	18.17±8.81	t=-0.361 p=0.719	58.66±19.90	t=0.490 p=0.625
No	27 (21.1)	18.85±8.08		18.88±7.34		18.85±7.78		56.59±17.97	

Number of children									
1	15 (11.7)	19.73±8.31	F=0.445 p=0.721	21.80±5.75	F=1.234 p=0.300	22.66±7.18	F=1.795 p=0.152	64.20±16.37	F=1.205 p=0.311
2	50 (39.1)	19.14±8.35		18.42±8.62		16.98±8.47		54.54±21.06	
3	39 (30.5)	20.10±7.64		21.12±7.07		18.74±8.46		59.97±17.49	
4 or over	24 (18.8)	21.41±7.73		20.20±8.05		17.70±9.32		59.33±20.45	
Kinship with spouse									
Yes	42 (32.8)	17.83±8.79	**t=-2.107 p=0.037**	17.88±8.37	**t=-2.154 p=0.033**	16.07±8.33	**t=-2.100 p=0.038**	51.78±20.88	**t=-2.679 p=0.008**
No	86 (67.2)	20.95±7.37		21.00±7.34		19.41±8.53		61.37±18.03	
Gender of disabled child									
Girl	53 (41.4)	21.28±7.49	t=1.625 p=0.107	20.00±7.80	t=0.028 p=0.977	19.16±8.20	t=0.941 p=0.348	60.45±19.57	t=1.089 p=0.278
Boy	75 (58.6)	18.97±8.20		19.96±7.84		17.72±8.84		56.65±19.35	
Total	128 (100)	19.92±7.97		19.97±7.80		18.32±8.58		58.22±19.46	

SD: Standard deviation, MSPSS: Multidimensional scale of Perceived Social Support scores

personal care or social relationships even though she is the primary person responsible for the child's care in extended families. In the study of Kırbaş and Özkan (23), mothers living in an extended family had higher mean scores of perceived social support from the family than for those mothers who lived in a nuclear family. Bahar et al. (24), reported that social the support needs of mothers living in an extended family were lower. The results of this study were found to be similar to the literature (24,25).

In this study, mothers who had kinship with their spouse had lower mean scores on the MSPSS and its subscales. The difference between them was statistically significant (Table I). This result can be explained by the fact that the families of the woman and man do not provide the required support because of the concern that they will have to take the responsibility for the disabled child's care in the future.

It was reported that those mothers who had difficulty in the child's care had lower mean scores on the MSPSS and its subscales (Table II). These mothers were having difficulty especially because of financial problems, the child's aggressive behavior and their unmet personal needs according to this study. It has been reported in related studies that mothers of children with a chronic disease or any kind of disability need more social support compared to fathers (22,26). This situation might be a reflection of the mothers' undertaking of the child care role to a greater extent. Kahriman and Bayat (27) determined that all of the parents had difficulty in the child's care and 26.7% received support for the care of their disabled child.

In the present study, it was determined that the relationships of one third of the mothers with their husbands and nearly one fourth of their relationships with their healthy children and relatives were affected (p>0.05, Table II). Similar to the results of the present study, the study of Aylaz et al. (7) revealed that having an autistic child negatively affected the relationships of family members with each other, couples did not allocate time for each other, their sharing reduced, and they blamed each other for a long time. Also, in their study, Kahriman and Bayat (27) found that mothers' relationships with their husband, other children, relatives and neighbors were negatively affected because they had a disabled child and the social support mean scores of these mothers whose relationships were negatively affected were lower.

Mothers who stated that their relationships with their relatives were not influenced because of having a disabled child, were found to have higher mean scores on the family

Table II. Comparison of difficulties experienced by the mothers due to having a disabled child, state of their relationships, and their MSPSS scores

		MSPSS							
		Significant other		Family		Friend		Total	
	n (%)	Mean ± SD	Test and sig.	Mean ± SD	Test and sig.	Mean ± SD	Test and sig.	Mean ± SD	Test and sig.
Having difficulty in care of child									
Yes	79 (61.7)	19.75±7.76	t=-0.306 p=0.760	19.60±7.75	t=-0.678 p=0.499	17.15±8.61	t=-1.978 p=0.050	56.51±18.96	t=-1.263 p=0.209
No	49 (38.3)	20.20±8.37		20.57±7.91		20.20±8.26		60.97±20.13	
Difficulties experienced									
Being extremely nervous, aggression	20 (25.3)	18.25±8.23	F=1.695 p=0.147	19.35±8.90	F=0.557 p=0.732	17.25±9.70	F=1.091 p=0.373	54.85±21.69	F=1.382 p=0.241
Personal care, dressing	11 (13.9)	23.90±7.75		19.27±9.40		21.36±7.33		64.54±16.09	
Inappropriate use of stuff	9 (11.4)	19.66±9.43		20.55±7.45		16.11±8.50		56.33±23.48	
Not leaving with someone when going out	6 (7.6)	17.83±6.40		18.00±5.69		12.66±8.61		48.50±18.39	
Communicating, obstinacy, yelling	12 (15.2)	23.16±5.28		22.66±6.67		18.75±6.95		64.58±9.98	
Financial problem, moral depression	21 (26.6)	17.66±7.39		18.33±7.18		15.66±8.88		51.66±18.56	
Affected relationship with their husbands									
Yes	29 (22.7)	17.44±8.85	t=-1.926 p=0.056	18.27±8.40	t=-1.339 p=0.183	16.96±8.55	t=-0.966 p=0.336	52.68±21.02	t=-1.756 p=0.082
No	99 (77.3)	20.65±7.59		20.47±7.58		18.71±8.59		59.84±18.78	
Way of being affected									
Separating bedrooms	8 (27.6)	19.12±8.80	F=0.417 p=0.743	20.87±7.67	F=0.378 p=0.769	18.25±7.49	F=0.222 p=0.880	58.25±19.76	F=0.247 p=0.863
Impaired communication	12 (41.4)	16.08±8.93		17.16±8.50		17.58±8.84		50.83±21.93	
Divorce	2 (6.9)	13.00±11.31		19.50±2.12		15.50±16.26		48.00±29.69	
Ignoring of spouse	7 (24.1)	19.14±9.49		16.85±10.63		14.85±8.93		50.85±22.76	
Affected relationship with healthy children									
Yes	25 (19.5)	19.64±8.14	t=-0.202 p=0.840	19.28±8.94	t=-0.496 p=0.621	17.40±8.74	t=-0.596 p=0.552	56.32±19.62	t=-0.544 p=0.587
No	103 (80.5)	20.00±7.96		20.14±7.53		18.54±8.56		58.68±19.49	
Affected relationship with relatives									
Yes	22 (17.2)	18.50±7.08	t=-0.924 p=0.357	16.68±8.96	**t=-2.210 p=0.029**	16.81±8.58	t=-0.902 p=0.369	52.00±20.22	t=-1.660 p=0.099
No	106 (82.8)	20.22±8.14		20.66±7.40		18.63±8.58		59.51±19.14	
Having financial difficulties									
Yes	73 (57.0)	19.02±7.91	t=-1.482 p=0.141	19.21±7.64	t=-1.268 p=0.207	16.36±8.80	**t=-3.123 p=0.002**	54.61±19.38	**t=-2.465 p=0.015**
No	55 (43.0)	21.12±7.96		20.98±7.96		20.90±7.60		63.01±18.68	

Causes of financial difficulties									
Child's being obliged to have special education	11 (15.1)	21.18±7.73	F=0.646 p=0.187	19.90±8.10	F=1.579 p=0.202	12.00±8.77	F=1.581 p=0.202	53.09±19.43	F=0.891 p=0.450
Health expenses	52 (71.2)	17.98±8.20		18.19±7.87		17.34±8.77		53.51±20.47	
Not going to school due to financial problem	4 (5.5)	18.25±5.18		24.00±4.89		12.25±9.53		54.50±6.65	
Not working because of not to leave child alone	6 (8.2)	24.66±4.36		23.66±2.94		18.66±7.14		67.00±12.23	
Receiving support for care of disabled child									
Yes	32 (25.0)	20.00±8.87	t=0.057 p=0.954	22.43±6.61	**t=2.298 p=0.025**	18.93±8.73	t=0.468 p=0.640	61.37±21.03	t=1.057 p=0.293
No	96 (75.0)	19.90±7.69		19.15±8.02		18.11±8.56		57.17±18.91	
Person/people proving support									
Spouse	2 (1.6)	28.00±0.00	F=1.201 p=0.328	28.00±0.00	F=2.607 p=0.071	28.00±0.00	F=1.333 p=0.283	84.00±0.00	F=2.170 p=0.114
Family	23 (18.0)	19.65±9.39		23.21±6.74		19.39±9.40		62.26±21.92	
Environment (neighbor, relative)	5 (3.9)	18.80±6.97		19.00±9.00		20.00±6.78		57.80±14.39	
Social services	2 (1.6)	11.50±2.12		11.50±2.12		10.50±4.94		33.50±4.94	
Total	128 (100)	19.92±7.97		19.97±7.80		18.32±8.58		58.22±19.46	

SD: Standard deviation, MSPSS: Multidimensional scale of Perceived Social Support scores

subscale of the MSPSS (Table II). This result indicates that perceived social support from the family had an important role in the relationships of these mothers. It is also emphasized in the literature that the mothers' religious beliefs could make a positive contribution to the marital relationship and behaviors among family members (28).

In this study, it was determined that those mothers who did not have financial problems had higher mean scores on the MSPSS and its friend subscale. There was a statistically significant difference between them (Table II). Studies revealed that families of children with special needs have a narrower social support network which is limited with family members and close friends (29). In this situation, it can be asserted that support by close family members and close friends, who are the only and the closest support group for parents, is important in this process. Karpat and Girli (30) determined that parents considered their families to be the social support source in the first rank, their friends in the second rank, and people within the significant other category in the third rank. "Significant other" was defined as a person other than family or friends (for example; girlfriend, boyfriend, fiancée, relative, neighbor, doctor). When considering the whole, the sample group utilized from special education, trainers also can be included in the "significant other" category specific to this study. As in this study, professionals to whom trainers and mothers have a relationship with, can be asserted to be functional as a social support source.

It was determined that the mothers had good level mean scores on the MSPSS and they had moderate level mean scores of its subscales in this study. Karadağ (29) reported that mothers with disabled children did not have adequate social support. It is important that parents with a disabled child receive social support from their surrounding, especially from relatives. This is because the behavior of the child and family and their development in terms of various aspects are positively influenced with good social support. At the same time, parents who share their responsibilities with other people are supported by the surrounding people and so think they are not alone allowing them to cope with the problems more easily (29).

Comparison of Some of the Mothers' Characteristics and the Maslach Burnout Inventory

In this study, more than half of the mothers were determined to have difficulty in the care of their ID child. The difference between those mothers who had financial problems due to the care of their children and the mean scores of the EE and DP subscales was statistically

Table III. Comparison of the mothers' socio-demographic characteristics and MBI scores

		MBI							
		EE		DP		PA		Total	
	Mean ± SD	**Mean ± SD**	**Test and sig.**	**Mean ± SD**	**Test and sig.**	**Mean ± SD**	**Test and sig.**	**Mean ± SD**	**Test and sig.**
Child's age	11.30±3.88	-	r=-0.075 p=0.397	-	r=-0.043 p=0.633	-	r=0.118 p=0.185	-	r=-0.008 p=0.928
Family's income level (TL)	761.23±524.66	-	r=-0.101 p=0.259	-	**r=-0.197 p=0.026**	-	r=0.028 p=0.755	-	r=-0.117 p=0.188
Mother's age	**n (%)**								
20-30 years	21(16.4)	15.85±7.68	F=1.295 p=0.278	5.80±4.44	F=0.746 p=0.476	7.57±4.41	F=1.295 p=0.278	29.23±10.82	F=0.183 p=0.833
30-40 years	55 (43.0)	13.56±7.91		5.00±4.24		9.83±4.93		28.40±12.65	
40 ↑ years	52 (40.6)	15.76±7.63		4.53±3.64		9.51±6.56		29.82±12.26	
Marital Status									
Married	121 (94.5)	14.76±7.71	t=-0.406 p=0.686	4.92±4.09	t=-0.228 p=0.820	9.38±5.72	t=0.370 p=0.712	29.07±12.15	t=-0.165 p=0.869
Single	7 (5.5)	16.00±9.46		5.28±3.14		8.57±2.87		29.85±12.87	
Educational level									
Illiterate	15 (11.7)	14.60±7.64	F=1.163 p=0.330	6.00±3.62	F=0.999 p=0.411	10.53±7.89	F=1.454 p=0.220	31.13±12.01	F=1.248 p=0.294
Primary school	84 (65.6)	14.70±8.08		4.82±4.14		8.72±4.24		28.25±12.21	
Secondary school	11 (8.6)	18.27±6.92		6.09±3.80		11.54±9.12		35.90±11.38	
High school	14 (10.9)	14.92±6.91		4.42±4.20		8.78±5.92		28.14±12.50	
University	4 (3.1)	8.75±4.85		2.25±2.62		13.50±6.85		24.50±9.14	
Family type									
Nuclear	110 (85.99	14.46±8.02	F=1.027 p=0.361	4.91±4.06	F=0.039 p=0.962	9.29±5.71	F=0.075 p=0.928	28.67±12.40	F=0.670 p=0.513
Extended	15 (11.7)	17.53±5.65		5.20±4.21		9.80±5.30		32.53±10.71	
Broken	3 (2.3)	15.00±7.00		4.66±3.05		8.66±4.04		28.33±8.38	
Employment status									
Yes	9 (7.0)	12.55±6.96	t=-0.911 p=0.364	4.22±3.73	t=-0.555 p=0.580	8.77±5.80	t=-0.309 p=0.758	25.55±12.58	t=-0.912 p=0.363
No	119 (93.0)	15.00±7.84		5.00±4.07		9.37±5.61		29.38±12.11	
Social security									
Yes	101 (78.9)	14.84±7.86	t=0.016 p=0.987	4.88±4.04	t=-0.346 p=0.730	9.70±6.10	**t=2.164 p=0.033**	29.42±12.39	t=0.555 p=0.580
No	27 (21.1)	14.81±7.63		5.18±4.08		7.96±2.73		27.96±11.27	

Number of children									
1	15 (11.7)	14.20±8.61	F=0.103 p=0.958	4.26±3.80	F=1.138 p=0.336	9.13±4.54	F=0.269 p=0.848	27.60±11.42	F=0.142 p=0.935
2	50 (39.1)	14.62±7.70		5.30±4.01		9.66±5.86		29.58±13.12	
3	39 (30.5)	15.35±7.64		5.46±4.56		8.71±5.04		29.53±12.02	
4 or over	24 (18.8)	14.83±8.11		3.79±3.18		9.79±6.65		28.41±11.21	
Kinship with spouse									
Yes	42 (32.8)	14.16±8.67	t=-0.678 p=0.499	4.95±3.98	t=0.014 p=0.989	10.14±6.48	t=1.140 p=0.256	29.26±12.88	t=0.094 p=0.925
No	86 (67.2)	15.16±7.34		4.94±4.08		8.94±5.11		29.04±11.84	
Gender of disabled child									
Girl	53 (41.4)	13.96±8.16	t=-1.068 p=0.288	4.67±3.77	t=-0.625 p=0.533	8.83±4.47	t=-0.858 p=0.393	27.47±12.65	t=-1.292 p=0.199
Boy	75 (58.6)	15.45±7.50		5.13±4.23		9.69±6.28		30.28±11.71	
Total	128 (100)	14.83±7.78	-	4.94±4.03	-	9.33±5.60	-	29.11±12.14	-

MBI: Maslach Burnout Inventory, EE: Emotional exhaustion, DP: Depersonalization, PA: Personal accomplishment, SD: Standard deviation

significant (Table IV). These results are important in terms of revealing the importance of being supported regarding physical and financial difficulties experienced by these mothers.

Those mothers who were ignored or divorced by their husbands had higher scores on the PA subscale (Table IV). This result can be asserted as an indicator for women's coping with difficulties in the absence of their husbands and the struggle to be successful. Having a disabled child creates new problems since it comes with responsibilities such as the care of the child, health, education, and social relations. Thus, couples experience burnout in their relationship. Even though the couples' burnout does not always lead to divorce, it reduces the quality of the relationship. In this case, they might perceive their whole relationship to be complicated and compelling (31). Improving marital satisfaction, co-parenting and parenting practices would reduce parental burnout. Hence, in cases where the child also suffers from a chronic disease, it may therefore be of particular importance for healthcare practitioners to emphasise the importance of shared parental responsibility to prevent stress and burnout in mothers (32).

In this study, it was determined that the MBI's mean score of those mothers whose relationships with their relatives were negatively affected were higher and the difference between them was statistically significant. These mothers with children exhibit high levels of stress, a high rate of psychological problems, and burnout. It is of great importance that mothers are supported in coping with these issues and maintaining their health in this context. It is stated that social support reduces stress, contributes to developing positive coping skills and diminishes burnout (33).

It was determined that mothers who had financial problems due to the special education of their child received higher mean scores on the EE and DP subscales and the difference between them were statistically significant. In the literature, financial difficulties increase stress and influenced mental health. It is pointed out that a family's financial status has an effect on the parents' coping with their child's limitations (33). Studies have demonstrated that carers for ID children experience additional psychological distress and depression compared to the parents of normal children. Some studies have also reported negative outcomes among the carers such as physical problems, social, as well as financial issues for the child's family. This often leads to marital breakdowns and divorce (34).

Table IV. Comparison of difficulties experienced by the mothers due to having a disabled child, state of their relationships, and their MBI score

		MBI							
		EE		DP		PA		Total	
	n (%)	Mean ± SD	Test and sig.	Mean ± SD	Test and sig.	Mean ± SD	Test and sig.	Mean ± SD	Test and sig.
Having difficulty in care of child									
Yes	79 (61.7)	15.96±7.77	**t=2.106 p=0.037**	5.49±3.94	**t=1.972 p=0.051**	9.07±5.26	t=-0.665 p=0.507	30.53±12.27	t=1.686 p=0.094
No	49 (38.3)	13.02±7.52		4.06±4.07		9.75±6.14		26.83±11.68	-
Difficulties experienced									
Being extremely nervous, aggression	20 (25.3)	16.05±7.73	F=0.525 p=0.757	6.70±3.79	F=1.207 p=0.314	8.55±5.23	F=0.403 p=0.845	31.30±13.14	F=0.713 p=0.616
Personal care, dressing	11 (13.9)	16.72±10.35		5.36±4.34		10.09±7.60		32.18±13.76	-
Inappropriate use of stuff	9 (11.4)	13.11±7.75		4.44±5.29		7.55±2.40		25.11±12.06	-
Not leaving with someone when going out	6 (7.6)	19.66±6.40		7.50±4.96		8.83±1.72		36.00±10.69	-
Communicating, obstinacy, yelling	12 (15.2)	15.66±6.74		4.00±3.01		8.66±3.91		28.33±9.69	-
Financial problem, moral depression	21 (26.6)	15.80±7.60		5.14±3.24		10.00±6.21		30.95±12.76	
Affected relationship with their husbands									
Yes	29 (22.7)	17.03±7.97	t=1.743 p=0.084	6.06±4.28	t=1.716 p=0.089	9.44±4.61	t=0.122 p=0.903	32.55±12.44	t=1.746 p=0.083
No	99 (77.3)	14.19±7.64		4.61±3.92		9.30±5.88		28.11±11.92	-
Way of being affected									
Separating bedrooms	8 (27.6)	16.00±5.87	F=0.439 p=0.727	7.62±3.50	F=0.546 p=0.655	7.00±2.50	**F=2.847 p=0.058**	30.62±8.63	F=0.771 p=0.521
Impaired communication	12 (41.4)	16.08±6.21		5.66±4.37		8.75±3.57		30.50±11.54	-
Divorce	2 (6.9)	16.00±12.72		4.00±5.65		10.50±2.12		30.50±20.50	-
Ignoring of spouse	7 (24.1)	20.14±12.00		5.57±5.06		13.14±6.51		38.85±16.11	-
Affected relationship with healthy children									
Yes	25 (19.5)	16.44±8.91	t=0.323 p=0.252	5.80±4.14	t=0.755 p=0.240	9.24±6.05	t=0.191 p=0.924	31.48±14.08	t=0.220 p=0.280
No	103 (80.5)	14.44±7.48		4.73±4.00		9.35±5.51		28.54±11.62	-
Affected relationship with relatives									
Yes	22 (17.2)	17.13±7.51	t=1.531 p=0.128	6.00±3.92	t=1.350 p=0.179	10.45±5.64	t=1.029 p=0.305	33.59±12.33	**t=1.919 p=0.057**
No	106 (82.8)	14.35±7.78		4.72±4.04		9.10±5.59		28.18±11.94	-

Having financial difficulties										
Yes	73 (57.0)	14.82±7.71	t=-0.023 p=0.981	4.83±3.86	t=-0.353 p=0.725	9.38±5.20	t=0.110 p=0.912	29.04±11.98	t=-0.081 p=0.935
No	55 (43.0)	14.85±7.94		5.09±4.29		9.27±6.13		29.21±12.45	-
Causes of financial difficulties									
Child's being obliged to have special training	11 (15.1)	20.27±8.62	**F=3.080 p=0.033**	7.63±4.24	**F=3.412 p=0.022**	9.36±5.14	F=0.504 p=0.681	37.27±11.98	F=2.410 p=0.074
Health expenses	52 (71.2)	13.71±7.40		4.00±3.48		9.36±5.38		27.07±11.76	-
Not going to school due to financial problem	4 (5.5)	18.75±6.23		6.25±3.77		7.00±2.16		32.00±10.09	-
Not having a job not to leave child alone	6 (8.2)	11.83±4.91		6.00±4.28		11.16±5.49		29.00±10.54	-
Receiving support for care of disabled child									
Yes	32 (25.0)	14.00±7.91	t=-0.700 p=0.485	4.78±3.89	t=-0.264 p=0.792	10.03±7.86	t=0.631 p=0.532	28.81±13.93	t=-0.149 p=0.882
No	96 (75.0)	15.11±7.76		5.00±4.10		9.10±4.64		29.21±11.56	-
Person/people proving support									
Spouse	2 (1.6)	18.00±7.07	F=0.741 p=0.536	7.00±4.24	F=0.634 p=0.599	13.00±8.48	**F=4.422 p=0.011**	38.00±19.79	F=1.478 p=0.242
Family	23 (18.0)	13.26±7.67		4.08±3.71		7.86±4.65		25.21±11.82	-
Environment (neighbor, relative)	5 (3.9)	11.20±5.01		3.60±2.30		19.80±13.47		34.60±16.51	-
Social services	2 (1.6)	18.50±6.36		6.00±2.82		11.50±0.707		36.00±2.82	-
Total	128 (100)	14.83±7.78	-	4.94±4.03	-	9.33±5.60	-	29.11±12.14	-

MBI: Maslach Burnout Inventory, EE: Emotional exhaustion, DP: Depersonalization, PA: Personal accomplishment, SD: Standard deviation

Correlation Between Multidimensional Scale of Perceived Social Support and Maslach Burnout Inventory scales

In this study, it was determined that there was a significant negative correlation between the mean scores received from the MBI and its EE and DP subscales and those received from the friend subscale. A negatively significant correlation was also found between the PA subscale and the family subscale (Table V). When examining correlations between the subscales of the scales used in the study, it was observed that the correlations of the subscales of the scales with each other were significant and high, and also the direction of correlations were in the expected direction according to the contents of the subscales. As the social support mothers received from their friends increased, their mean scores of EE, DP, and MBI decreased; as the social support recieved from the family increased, their mean scores of the PA subscale decreased. The results of the study were found to be similar to the information stated in the literature and revealed that social support decreases burnout levels.

It was determined in this study that those mothers who were having difficulty in the care of their child experienced burnout more. Generally, it supports the results indicating that having inadequate social support could cause burnout and emotional exhaustion is associated with friendship sources. Social support has a more important place in the lives of families who have a disabled child when compared to other families. It was also shown that the failure to adequately benefit from the perceived social support from friends was associated with emotional exhaustion, depersonalization and burnout (4). Duygun (35) stated that one of the factors related to emotional exhaustion of mothers who have an ID child was the search for social support.

Perceived social support (spouse, neighbor, family, relative, people

Table V. Evaluation of correlation between Multidimensional Scale of Perceived Social Support scores and Maslach Burnout Inventory scales

	Emotional exhaustion	**Depersonalization**	**Personal accomplishment**	**Total MBI**
Significant other	r=-0.039 p=0.660	r=-0.102 p=0.253	r=0.005 p=0.957	r=-0.057 p=0.524
Family	r=0.010 p=0.910	r=-0.074 p=0.403	**r=-0.216** **p=0.014**	r=-0.118 p=0.185
Friend	**r=-0.178** **p=0.044**	**r=-0.180** **p=0.042**	r=-0.040 p=0.657	**r=-0.192** **p=0.030**
Total MSPSS	r=-0.091 p=0.308	r=-0.151 p=0.089	r=-0.102 p=0.252	r=-0.155 p=0.080

MBI: Maslach Burnout Inventory, MSPSS: Multidimensional Scale of Perceived Social Support

subsidizing, friends) have a protective effect on the psychological health and well-being and a positive effect on preventing burnout. One of the most important factors in preventing burnout is to take short breaks from the work performed by mothers in order to refresh their intellectual and emotional resources (36).

Conclusion

In this study, more than half of mothers were determined to have difficulty in the care of their ID child. Mothers were found to have difficulty mostly due to financial problems and the aggressive behavior of the child. The relationships of one third of the mothers with their husbands and one fourth with their healthy children and relatives were affected negatively. A positive significant correlation was determined between the family's income level and the MSPSS, significant other and friend subscales of the scale. The burnout levels of those mothers who had difficulty in the care of their ID children, had only graduated from secondary school, had an extended family, were unemployed, used social security and had an ID boy were found to be higher. In this study, while higher MSPSS scores of the mothers were good it was unwanted stiuation their burnout levels were above the mean.

In accordance with the results obtained from the research; it is recommended to determine the multiple factors causing burnout in mothers of ID children through different studies to be conducted on this subject, to support mothers by using a multi-factorial team approach towards this goal, to positively change the perception of society regarding ID children, to increase the number of official institutions to be utilized by these children in terms of special education and social aspects and the number of employees, to provide counseling services to support the mother and child, to extend the context of legal regulations with government support, and for mothers to take short vacations and participate in activities they enjoy.

Ethics

Ethics Committee Approval: Ethics approval was received from Karadeniz Technical University Faculty of Medicine Scientific Research Ethics Committee (approval number: 24237859-179, date: 03.21.2014).

Informed Consent: Written permission from The Rehabilitation Centers in the city of Trabzon, and verbal consent from the participants were received.

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Authorship Contributions

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

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Original Article

Congenital Heart Diseases Detected by Prenatal Fetal Echocardiography and Associated Extracardiac Anomalies

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ABSTRACT

Aim: The aim of this study is to determine the relationship between extracardiac abnormalities and congenital heart diseases in fetuses that were referred for fetal echocardiography due to a variety of reasons.

Materials and Methods: A total of 1,158 pregnant woman whose fetal echocardiograms and detailed fetal anomaly scanning were performed between June 2017 and July 2018 were included in this study. The documents of the pregnant women were reviewed retrospectively. Those fetuses who were determined to have various organ anomalies and congenital heart defects were recorded.

Results: While 664 pregnant women were in the low-risk group, 494 pregnant women were in the high-risk group in the study. Congenital heart defects were detected in a total of 38 pregnant women (3.28%). The prevalence of all gastrointestinal system, urinary system and central nervous system anomalies were 5.35%, 3.79% and 6.73%, respectively. Interventricular septum, aorta, pulmonary and tricuspid valves associated with congenital heart diseases were found to be mostly related with these organ anomalies.

Conclusion: Gastrointestinal system and central nervous system anomalies were found to be mostly associated with congenital heart diseases. Also, the interventricular septum, aortic, pulmonary and tricuspid valves' anomalies were the most frequently detected congenital heart diseases in these situations.

Keywords: Fetal echocardiography, fetal anomaly scanning, congenital heart diseases, extracardiac anomalies

Introduction

Congenital heart diseases are common in neonates, complicating approximately 1% of live births (1). At the same time, the risk increases with fetal abortion and peripartum fetal death. Additionally, congenital heart diseases are the most common cause of death due to prenatal congenital anomalies (2). Therefore, the early detection of congenital heart diseases allows for reliable peripartum treatment strategies (3). Also, the detection of congenital heart diseases in the prenatal period has been demonstrated to improve survival after surgery

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and neurological outcomes in neonates (4). The survey of congenital heart diseases in the perinatal period depends on the associated extra cardiac organ anomalies, chromosomal anomalies, legal differences in each of the countries and the families' desire for the baby (5). Today, fetal echocardiography is increasingly used in the prenatal diagnosis of congenital heart diseases. Pregnancies with fetal, maternal or hereditary reasons for fetal echocardiography are considered to be high-risk groups (6,7). Additionally, suspicion of fetal congenital heart disease in the second trimester or the detection of any anomaly in extracardiac organs are the other indications for fetal echocardiography (8). In recent years, there have been reports that the diagnostic sensitivity of fetal echocardiography has increased by up to 78-98% (9-11).

Extra cardiac anomalies are associated with congenital heart diseases in one fifth of cases, and there is also a high association with aneuploidy on prenatal testing in up to one quarter of cases (12). Currently, there are well-defined chromosomal anomalies such as trisomy 21 associated with congenital heart diseases like atrioventricular septal defect. However, there are limited studies on the association of congenital heart diseases and extracardiac organ anomalies (13-17). The aim of this study is to determine the risk groups in those pregnancies who were sent for fetal echocardiography and to identify the associations between congenital heart diseases and extra cardiac organ anomalies.

Materials and Methods

Study Population

This retrospective study was performed between June 2017 and July 2018 and 1,158 pregnant women who were in the 18th to 22nd week of gestation were included in the study. The patients in our study consisted of pregnant women referred by obstetricians, having a previous child or family history of cardiac anomaly and those who were self-referral. All the data of these pregnant women were analyzed in detail for pregnancy history, reasons for referral to our clinic, any drug usage, presence of family history, number and characteristics of previous pregnancies, presence of chromosomal or fetal anomalies and congenital or acquired heart diseases in the family. Also, ultrasonographic fetal anomaly scanning results including any extra cardiac organ anomaly were recorded. The pregnancies were grouped as either high-risk or low-risk pregnancies and compared in terms of congenital heart diseases and extra cardiac organ anomalies.

Fetal Echocardiography

Fetal echocardiography was performed with Philips Affiniti 50 (Philips Healthcare, Andover, Netherlands) by the same observer and an echocardiographic scanner with 2.5-5 MHz transducers was used. The fetal examination included the standard techniques to evaluate the position and axis of the heart and for scanning plans and conventional Doppler and M-mode measurements (8-10). The structural disorders of the heart were evaluated by a two-dimensional ultrasound imaging technique and the rhythm and dimensions of the heart were evaluated by the M-mode technique. Echocardiography procedure was repeated several times on those pregnant women who had unclear ultrasound imaging, dysrhythmia, fetuses with congenital heart diseases or extra cardiac organ anomalies and those with poly-pregnancies. Also, prenatal counseling was provided for chromosome anomalies in patients with congenital heart disease detected by fetal echocardiography.

Perinatal Follow-up and Fetal Anomaly Scanning

Detailed fetal ultrasonography was performed on all of the pregnant women who were included in the study between the 18th and 22nd weeks of gestation. Fetal anomaly scanning was performed by the same radiologist and obstetricians with an ultrasonography device (Philips Affiniti 50, Philips Healthcare, Andover, Netherlands) using 2.5-5 MHz transducers and extra cardiac organ anomalies were recorded in detail (12,13). Amniocentesis, chorionic villous sampling or cordocentesis was performed for the detection of chromosomal anomalies according to the gestational week in appropriate cases. Also, the ultrasonography procedure was repeated several times on those pregnant women who had unclear ultrasound imaging, dysrhythmia, fetuses with congenital heart diseases or extra cardiac organ anomalies and those with poly-pregnancies.

Statistical Analyses

All statistical analyses were performed using SPSS for Windows Version 17.0 software (Chicago, IL, USA). The prevalence of congenital heart diseases in low-risk and high-risk pregnancies was compared using the chi-square test. Quantitative variables are expressed as mean ± standard deviation, and qualitative variables are given as frequency and percentage. Statistical significance was inferred at $p<0.05$.

Results

A total of 1,158 pregnant women on whom fetal echocardiography was performed were included in the study.

The pregnancies were classified as low-risk and high-risk groups according to criteria during referrals (Table I). In this way, 664 (57.34%) pregnant women were classified as the low-risk group while 494 (42.66%) pregnant were classified as the high-risk group. In the low-risk group, the largest group were seen to be self-referral (27.73%). However, fetal organ anomalies (14.16%), maternal diabetes (11.83%), and history of familial congenital heart diseases (1.81%) were the most common reasons for referral in the high-risk group.

The mean ages were 26.65±8.52 and 27.21±12.45 years in the low-risk and high-risk groups, respectively and no statistically significant difference was found between the two groups (p>0.05) (Table II). The mean gestational week was 21.23±1.54 and 21.81±2.09 weeks in the low-risk and high-risk groups, respectively. Also, no statistical difference was detected for gestational weeks between the two groups (p>0.05). Primiparas were in the majority in both groups. Additionally, 21 and 19 pregnancies were for twins in the low-risk and high-risk groups, respectively.

In the low risk group; ventricular septal defect, atrioventricular septal defect, and hypoplastic left heart were detected in 5 cases (0.75%), 1 case (0.15%) and 1 case (0.15%), respectively. On the other hand, in the high risk group; ventricular septal defect atrioventricular septal defect was detected in 12 cases (2.42%), Atrioventricular septal defect in 5 cases (1.01%), aortic stenosis in 2 cases (0.40%), double outlet right ventricle in 2 cases (0.40%), pulmonary atresia/hypoplasia in 4 cases (0.81%), hypoplastic left heart syndrome in 3 cases (0.61%), aortic coarctation/aortic arch hypoplasia in 1 case (0.20%), Ebstein anomaly in 1 case (0.20%) and tricuspid atresia in 1 case (0.20%) (Table III). In this way, the prevalence of congenital heart diseases in our series was found to be 1.05% and 6.25% in the low-risk and high-risk pregnancies respectively while the overall prevalence was 3.28%. Amniocentesis samples were performed on 25 pregnant women in the high-risk group and 5 of them had chromosomal anomalies (trisomy 21).

A complete atrioventricular block was detected in two pregnancies in the high-risk group. Also, one of them had mixed connective tissue disease while the other had no diseases rheumatologically and the fetal arrhythmia turned into sinus rhythm in this pregnancy. Additionally, premature atrial beats and supraventricular tachycardia were detected in 8 and 1 pregnant women in the high-risk group and low-risk groups, respectively.

Fetal anomaly scanning with ultrasonography revealed; esophagus atresia in 3 cases, duodenal atresia in 2 cases,

Table I. Distribution of pregnant women according to low-risk and high-risk factors

Risk groups and factors	n (1.158)	%
Low-risk		
Suspicion of CHD during 2nd trimester ultrasound	283	24.43
Self-referral	321	27.73
Lack of good image of the fetal heart by ultrasound	60	5.18
Total	664	57.34
High-risk		
Maternal factors		
Maternal diabetes	137	11.83
Maternal use of medicine	21	1.81
Advanced maternal age	35	3.02
Maternal CHD	5	0.43
Maternal rheumatologic diseases	3	0.25
Maternal TORCH diseases	0	0
Fetal factors		
Dysrhythmia	11	0.94
Polyhydramniosis, oligohydramniosis	35	3.02
Immune/non immune hydrops	3	0.25
Fetal extracardiac anomaly	164	14.16
Chromosomal anomaly	12	1.03
Increased nuchal translucency	13	1.12
Hereditary factors		
Previous child or fetus with CHD	15	1.29
Previous child or fetus with extracardiac anomaly	19	1.64
Familial CHD (excluding parents and siblings)	21	1.81
Total	494	42.66

CHD: Congenital heart diseases, TORCH: Toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus

Table II. The demographic data of pregnant women

	Low-risk (n=664)	High-risk (n=494)	p value
Age (years)	26.65±8.52	27.21±12.45	>0.05
Gestational week (weeks)	21.23±1.54	21.81±2.09	>0.05
Primipara (n/%)	434/65.36	298/60.32	>0.05*
Multipara (n/%)	209/31.48	177/35.83	>0.05*
Multiple pregnancy (n/%)	21/3.16	19/3.84	>0.05*

*Student t-test

fetal echogenic bowel in 57 cases, dilatation of the urinary system in 34 cases, renal agenesis in 10 cases and intracranial ventricle dilatation (hydrocephalus) in 78 cases (15.88%). The prevalence of all gastrointestinal system, urinary system and central nervous system anomalies were 5.35%, 3.79% and 6.73%, respectively. The associated congenital heart diseases which were detected in these pregnant women are given in Table IV. Ventricular septal defect and aortic coarctation/aortic arch hypoplasia were detected in two of the esophageal atresia fetuses (33.33%). Additionally, atrioventricular septal defect was determined in one of the fetuses with duodenal atresia (50%). Also, ventricular septal defect was detected in four, atrioventricular septal defect in one, aortic stenosis in one, hypoplastic left heart syndrome in one and tricuspid atresia in one of the fetuses who had echogenic bowel (14.03%). Fetal echocardiography of the fetuses with urinary system dilatation revealed ventricular septal defect in three, double outlet right ventricle in one, pulmonary atresia/hypoplasia in one, hypoplastic left heart syndrome in one and Ebstein anomaly in one of the fetuses (20.58%). Ventricular septal defect and pulmonary atresia/hypolasia were detected in two of the fetuses with renal agenesis (20%). Additionally, ventricular septal defect was detected in three cases, atrioventricular septal defect in one, double outlet right ventricle in one, pulmonary atresia/hypoplasia in one, hypoplastic left heart syndrome in two and aortic coarctation/aortic arch hypoplasia in one case of those fetuses with intracranial ventricle dilatation (hydrocephalus) (11.53%).

Echogenic bowel and dilatation of urinary system anomalies were detected in two of Trizomi 21 fetuses. Among these two fetuses, atrioventricular septal defect was determined in one and ventricular septal defect was determined in the other.

Table III. Distribution of congenital heart diseases according to risk groups

Congenital heart disease	Low-risk (n=664) (n/%)	High-risk (n=494) (n/%)
Ventricular septal defect	5/0.75	12/2.42
Atrioventricular septal defect	1/0.15	5/1.01
Aortic stenosis	0/0	2/0.40
Double outlet right ventricle	0/0	2/0.40
Pulmonary atresia/hypoplasia	0/0	4/0.81
Hypoplastic left heart syndrome	1/0.15	3/0.61
Aortic coarctation/aortic arch hypoplasia	0/0	1/0.20
Ebstein anomaly	0/0	1/0.20
Tricuspid atresia	0/0	1/0.20
Total	**7/1.05**	**31/6.25**

Discussion

In this study, fetal echocardiography was performed on 1,158 pregnant women and the prevalence of congenital heart diseases was determined to be 3.28%. Complex congenital heart diseases and fetal arrhythmias were also determined in our series. Additionally, these congenital heart diseases were at higher rates in the high-risk group compared to the low-risk pregnancies group.

Table IV. The association between congenital heart diseases and extracardiac anomalies

	Extracardiac anomaly					
Congenital heart disease	**Esophagus atresia (n=3)**	**Duodenal atresia (n=2)**	**Echogenic bowel (n=57)**	**Dilatation of urinary system (n=34)**	**Renal agenesis (n=10)**	**Intracranial ventricle dilatation (n=78)**
Ventricular septal defect	1		4	3	1	3
Atrioventricular septal defect		1	1			1
Aortic stenosis			1			
Double outlet right ventricle				1		1
Pulmonary atresia/hypoplasia				1	1	1
Hypoplastic left heart syndrome			1	1		2
Aortic coarctation/aortic arch hypoplasia	1					1
Ebstein anomaly				1		
Tricuspid atresia			1			
Total (%)	**1 (33.33)**	**1 (50)**	**8 (14.03)**	**7 (20.58)**	**2 (20)**	**9 (11.53)**

Nowadays, the frequency of fetal anomaly scanning with ultrasonography is increasing and the most common referral indication for fetal echocardiography that has the greatest positive yield of fetal congenital heart diseases is that of abnormal fetal anomaly scanning (13). Similarly, in our study, fetal anomaly was found to be the major indication of fetal echocardiography in the high-risk pregnancies group (14.16%). Also, other reasons were less frequent indications for fetal echocardiography in this group. Therefore, this finding suggests that performing fetal echocardiography during the fetal anomaly scanning is important in detecting congenital heart diseases. Our study revealed that the most common associated organ anomalies to congenital heart diseases were gastrointestinal (5.35%) and central nervous system (6.73%) anomalies. Similarly, in a comprehensive study of 1,262 pregnancies by Mone et al. (13), congenital heart diseases were reported to be associated more commonly with gastrointestinal (21.7%) and neurological system (28.3%) anomalies. In this context, similar studies have reported the existence of compatible results with the data in our study (14-16). However, Egbe et al. (17) reported that congenital heart diseases were more commonly associated with genitourinary and pulmonary system anomalies and these congenital heart diseases were also more commonly associated with cardiac septum, pulmonary, tricuspid and aortic valves. In our study, it was shown that congenital heart diseases including interventricular septum, tricuspid and aortic valve anomalies were more commonly associated with gastrointestinal system anomalies. On the other hand, our study revealed that congenital heart diseases including interventricular septum, pulmonary and aortic valve anomalies were found to be more commonly associated with central nervous system anomalies. As in the study of Egbe et al. (17), in our study, we reported that congenital heart diseases including cardiac septum, pulmonary and tricuspid valve anomalies were most commonly associated with genitourinary system anomalies.

Various chromosomal anomalies were also detected in our study. However, this number is limited and amniocentesis was not performed for all of the indicated gestations. Therefore, they could not be considered as a separate group. In these gestations, echogenic bowel and dilatation of urinary system anomalies were detected with atrioventricular and ventricular septal defects of congenital heart diseases.

Congenital heart disease is the leading cause of mortality in the neonatal period. Also, the presence of chromosomal or extra cardiac organ anomalies increases this mortality and affects the prognosis with treatment (15). Nowadays, the early detection of fetal organ anomalies with various ultrasonography techniques is increasing in experienced hands. Therefore, this situation may lead to early diagnosis, appropriate treatment and good prognosis.

Conclusion

In our study, the relationship between congenital heart diseases and extra cardiac organ anomalies indicates the importance of fetal echocardiography and detailed fetal anomaly scanning. Additionally, gastrointestinal and central nervous system anomalies are more frequently associated with congenital heart diseases, and interventricular septum, aortic, pulmonary and tricuspid valve anomalies are the most common congenital heart diseases detected in these conditions.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: H.A., M.K., B.S., C.B., Design: H.A., A.M.E., E.K.A., Fetal Echocardiography: H.A., Ultrasonography: M.K., B.S., C.B., M.S.. Data Collection or Processing: H.A., A.M.E., E.K.A., Analysis or Interpretation: M.K., B.S., C.B., M.S., Literature Search: H.A., M.S., Writing: H.A.

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Original Article

Efficacy and Safety of Intranasal Midazolam Versus Chloral Hydrate as Sedation for Quality Computed Tomography Imaging in Children

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ABSTRACT

Aim: The purpose of this study was to compare the efficacy and safety of aerosolized intranasal midazolam (INM) compared to oral chloral hydrate (OCH) as procedural sedatives in pediatric patients undergoing computed tomography (CT) imaging.

Materials and Methods: A prospective, randomized, double-blind clinical trial was utilized in children aged 1 to 8 years who presented to the ED with minor head trauma and were scheduled to undergo brain CT scan. One hundred and sixty children were randomized to receive INM 0.3 mg/kg with oral placebo or 75 mg/kg OCH with intranasal placebo. If the patient was not adequately sedated 20 minutes after the initial dose, a second dose of the same medication at one-third of the initial dosage was given. The sedation level of patients after drug administration was assessed using the Ramsay sedation scale.

Results: Both groups were comparable with respect to age, male to female ratio, weight, and baseline vital signs. Sixty two children (77.50%) in the INM group and 59 children (73.42%) in the OCH groups reached a Ramsay score of four, respectively (p=0.55). There was no significant difference in regards to the time to become adequately sedated (21.32±6.54 vs 23.62±7.40, p=0.173) and time for completing CT scan (30.37±7.18 vs 32.96±7.85, p=0.185). However, the time to recovery was shorter for the INM group (72.52±10.17 vs 88.10±10.27, p=0.001). No serious side effects were seen in the study groups (p=0.836). The majority of parents were somewhat to very satisfied, 83.54% and 81.25% in the OCH and INM groups, respectively (p=0.928).

Conclusion: INM can be used to sedate children between 1 to 8 years who are to undergo CT imaging of brain with a comparable rate of efficacy and safety to OCH.

Keywords: Chloral hydrate, computerized tomography, conscious sedation, intranasal midazolam

Introduction

In order to obtain useful data from accurate imaging without excessive radiation exposure, a child needs to be lain down during the scanning procedure. The imaging tests that are affected negatively by motion [computed tomography (CT) or magnetic resonance imaging] are the most common procedures for which children undergo sedation (1-3). Imaging can often be performed without sedation in older cooperative children and young infants (up to six months of age) who are swaddled and recently fed (1-4). It is difficult to keep younger children still during

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the time they need to get a scan. For CT, the child needs to lie still for 10-15 mins (3). There are several methods that can be used to limit the movement of a child during scanning.

Sedation has become more common for children undergoing imaging procedures. Adequate procedural sedation (PS) reduces patient's anxiety, reduces parental emotional distress and facilitates the ease, accuracy and the completion of the procedure (1,4). When a child is kept still long enough to obtain the necessary imaging, a successful sedation is assumed (5). A wide range of sedative medications are available for pediatric procedural sedation and analgesia (PSA) (6,7). The choice of drug and the targeted depth of sedation depends on the type of procedure and the patient's underlying medical condition (1-4). The ideal PSA agent should be one that has a quick onset of action, rapid recovery, few side effects, short and sufficient duration of action, provides airway protection, and has minimal effects on hemodynamics (8,9). Effective sedation may be given by several routes: Intravenous (IV) and oral, rectal, intranasal, transcutaneous, intramuscular and inhalation.

Oral chloral hydrate (OCH) is one of the first synthetic sedative agents, which has been considered as a sedative agent in pediatric patients for imaging, and it has been successfully given with other sedative agents (10-12). OCH produces effective sedation in 80-90% of patients (13). No significant adverse effects on cardiovascular or respiratory function have been reported at therapeutic doses (12,14). The main disadvantage is gastric irritation, which can lead to vomiting.

Midazolam has become the benzodiazepine of choice in PSA, with a more rapid onset and offset of effect (15,16). Midazolam is approved for many routes, including oral, IV, IM, rectal and intranasal (15-17). Intranasal Midazolam (INM) has got some advantages. INM can be rapidly absorbed through the highly vascularized nasal mucosa, resulting in a rapid and reliable onset of action. The shorter half-life, ease of administration, predictability and increased bioavailability by circumventing first-pass metabolism makes it a useful drug in the ED setting (17-21).

The dose of INM used in different studies range between 0.2 mg/kg and 0.5 mg/kg. The most common adverse effects reported following INM are burning or irritation in the nose and a bitter taste in the mouth (17-23). Aerosolized administration of midazolam on mucosal surfaces may enhance drug delivery. Aerosolized rather than drip administration of INM may decrease discomfort and improve tolerance of this route (24,25).

In this study, we compared the efficacy, safety, and recovery time of aerosolized INM and OCH as procedural sedatives in pediatric patients undergoing CT imaging. We evaluated the successful sedation rate, time to achieve sedation, sedation duration, and side effects.

Materials and Methods

Study Design and Setting

This study was designed as a prospective, randomized, parallel group, double-blinded placebo-controlled clinical trial. The study was conducted between September 2017 and June 2018 at Al-Zahra and Kashani Hospitals, two university hospitals in Isfahan/İran. This study was approved by the ethics committee of Isfahan University of Medical Sciences (approval number: IR.MUI.REC.1396.3.516) and was registered in the Iranian Registry of Clinical Trials under the number (IRCT20180129038549N4). Informed written parental consent was obtained before enrolling children into the study.

Participants

We enrolled a appropriate sample of children aged 1 to 8 years who presented to the ED with minor head trauma, were scheduled to undergo brain CT scan and who were determined by their physicians to require sedation. A complete history and physical examination determined all enrolled children as American Society of Anesthesiology class 1 (a normally healthy patient) or 2 (a patient with mild systemic disease e.g. mild asthma, controlled diabetes mellitus).

Children with any of the following criteria were excluded from the study: A history of developmental delay, underlying neurologic abnormality or autism; receiving a sedative hypnotic agent within the previous 48 hours; presence of gastritis or any other serious systemic disease; nasal allergy to drugs; obesity (body mass index >30), known contraindications to the use of the study drugs (e.g. hypersensitivity).

Study Protocol

We used a computer-generated random number table, which maintained allocation concealment, to randomize children into two groups. Randomization and double blinding of medication use was done by an independent investigator who was concealed from the study investigators. Neither the patients who received the drugs nor their parents, nor any of the investigators who administered the drugs, nor the health care providers knew the active component of the study medication. Data collectors and data analysts were all kept blinded to the allocation.

After ensuring informed consent, the patient's demographics (weight, height, age, gender) were recorded. The patient's initial vital signs including respiratory rate (RR), heart rate (HR), and pulse oximetry (O_2 saturation) were documented.

The children were randomly divided into two groups: Namely the OCH group and the INM group. The OCH group received 75 mg/kg OCH (100 mg/mL, Merck KGaA Company, Germany) with 0.3 mg/kg of intranasal placebo and the INM group received 0.3 mg/kg INM (5 mg/mL, Tehran Shimi Company, Iran) with an oral 75 mg/kg placebo. The sedation level of the patients after drug administration was assessed using the Ramsay sedation scale (RSS) (5,9,10,19). A score of four is considered as adequately sedated. If the patient was not adequately sedated 20 minutes after the initial dose, a second dose of the same medication at one third of the initial dosage was given. In case of failure to create an adequate sedation within 40 minutes, the patient was excluded from the study.

The RSS and vital signs (oxygen saturation, HR and RR) were examined at 10, 15, 20, 25, 30, 40, 60 and up to 180 minutes as needed in the studied patients.

Placebos were prepared for INM and chloral hydrate syrup. Every child received both a spray and a syrup so that the chance of receiving either drug was equal. The drugs were prepared and packed by the pharmacist. Each package contained a nasal spray and syrup. The packets were marked A or B following the codes according to the randomization. In one packet, there were INM and oral placebo, and in another packet, there were an equal volume of chloral hydrate syrup and the intranasal placebo. The patients and their parents, nurses, health care providers, researchers, data collectors, and outcome assessors and data analysts were blind to the allocation.

Outcome

The primary outcome measurement was the efficacy to induce adequate sedation to complete the CT scan. Adequate sedation was determined by the study nurse or physician.

A secondary outcome was the side effects (oxygen saturation of less than 90%, the need for assisted ventilation, vomiting, intractable irritability and agitation, laryngospasm, bradycardia and paradoxical agitation). The time from administration of the sedative drugs until adequate sedation, complete imaging and recovery criteria for discharge were also recorded. Recovery criteria included the return to baseline alertness, ability to maintain a patent airway, and the ability to sit up for 10 seconds or longer.

Parent satisfaction on a Likert scale (very satisfied, somewhat satisfied, unsure, somewhat dissatisfied, very dissatisfied) was evaluated by a study team member (19).

Statistical Analysis

Statistical analysis was performed using the SPSS 20.0 (IBM, Chicago, IL, USA). Chi-square test or Fisher exact test was used for data analysis of qualitative variables and mean values were compared using the independent t-test. All demographic and clinical variables were summarized using count and percentage n (%) for categorical variables and means plus or minus standard deviations for continuous variables. $P<0.05$ was determined to indicate statistical significance.

Results

One hundred and sixty children were entered into the study and 159 patients were analyzed. The patients of the two groups (INM and OCH) had comparable age, male to female ratio, weight, and baseline vital signs (Table I). Sixty-two children (77.50%) in the INM group and 59 children (73.42%) in the OCH groups reached a Ramsay score of four, respectively (p=0.55). The acquired Ramsay sedation score was 3.95±0.618 and 3.82±0.655 in the INM and OCH groups respectively (p=0.648) (Table II).

All children received an initial dose of medication, 33 (41.25%) patients in the INM group and 29 (36.71%) patients in the OCH group required a second dose (p=0.627).

No difference was noted between the 2 study groups in regards to the time to become adequately sedated (p=0.173) and time to completion of CT scan (p=0.185). However, the

Table I. Demographic and baseline characteristics of the children

Characteristics	Midazolam, n=80	Chloral hydrate, n=79	p value
Age (y)	3.8500±1.72913	3.8354±1.7572	0.958
Sex			
Male (%)	53 (66.25%)	51 (64.56%)	0.932
Female (%)	27 (33.75%)	28 (35.44%)	
Weight (kg)	14.7750±3.63518	14.2911±3.77628	0.878
Heart rate, bpm	105.33±16.84	103.58±16.91	0.513
Respiratory rate	22.38±1.97	23.24±2.04	0.645
Oxygen saturation, %	98.63±0.93	98.46±1.03	0.334

time to recovery was shorter for the INM group (p=0.001) (Table II).

No serious side effects were seen in our study groups. Side effects including a decrease in O2 saturation ≥10% below baseline, vomiting, and paradoxical agitation were the same between the two groups (p=0.836). The majority of parents were very to somewhat satisfied, 83.54% and 81.25% in the OCH and INM groups, respectively (p=0.928) (Table II).

There was no need for any invasive resuscitation. Oxygen saturation, HR and RR showed no significant differences before and after sedation in both groups (Table III).

Table II. Comparison of primary and secondary outcomes

Outcomes	Midazolam	Chloral hydrate	p value
Adequately Sedated[1]	62 (77.50%)	59 (73.42%)	0.55
Second dose[1]	33 (41.25%)	29 (36.71%)	0.627
Acquired Ramsay sedation score[2]	3.95±0.62	3.82±0.66	0.648
Time to sedation (minimum)[2]	21.32±6.54	23.62±7.40	0.173
Time to completion of CT scan (min)	30.37±7.18	32.96±7.85	0.185
Time to recovery (minimum)[2]	72.52±10.17	88.10±10.27	0.001
Side effects[1]	10 (14.28%)	8 (10.12%)	0.836
Vomiting	6 (7.6%)	6 (7.6%)	-
Decreased O_2 saturation	2 (2.5%)	2 (2.5%)	-
Paradoxical agitation	2 (2.5%)	0 (0%)	-
Parental satisfaction[1]	-	-	0.928
Very satisfied	25	27	-
Somewhat satisfied	40	39	-
Unsure	12	10	-
Somewhat dissatisfied	3	2	-
Very dissatisfied	0	1	-

[1]Number (%), [2]Mean ± standard deviation

Discussion

Appropriate sedation for children undergoing imaging in the ED is an important attribute for providing quality care and parental satisfaction. In this double blinded, placebo controlled randomized clinical study, the clinical effectiveness, safety, and potential side effects of OCH versus INM for pediatric sedation for brain CT scan were compared. The findings from this study show that 0.3 mg/kg of INM has comparable efficacy to 75 mg/kg chloral hydrate orally for sedation in children between the ages of 1 year and 8 years who underwent imaging.

Adequate sedation was achieved in 77.50% of the children who used INM compared with 73.42% for those who were given OCH. As in our study, Mekitarian Filho et al. (26) showed that the use of Aerosolized INM produced sedation in 76% of children within 20 minutes. Dallman et al. (27) showed an equal efficacy between INM (0.2 mg/kg) and chloral hydrate (62.5 mg/kg), although the latter caused longer sedation. However, Fallah et al. (5) showed that OCH was more effective than INM (93.3% vs 40%) in sedation induction in uncooperative children undergoing CT scan. The lower efficacy of midazolam in that study may be related to the low dose of 0.2 mg/kg. Stephen et al. (21) concluded successful sedation leading to completion of procedure was achieved in 95% of children with chloral hydrate compared with 51% for INM. Probably the differences between individuals, race and age range of the patients led to these differences.

Our study demonstrates a faster recovery time with INM versus chloral hydrate, similar to studies by Wheeler et al. (28), and Dallman et al. (27) while in contrast to Stephen et al. (21) Dallman et al. (27) and Wheeler et al. (28) showed that patients sedated with INM slept less and recovered more quickly than patients sedated with OCH, but Stephen et al. (21) showed that a significant difference in time to recovery was noted in the chloral hydrate group (78 minutes) versus the INM group (108 minutes).

The time to become adequately sedated and time to completion of CT scan was comparable between the 2

Table III. Comparison of physiologic parameters

Parameter	Before sedation			After sedation		
	Midazolam	Chloral hydrate	p value	Midazolam	Chloral hydrate	p value
Heart rate, bpm	105.33±16.84	103.58±16.91	0.513	104.38±15.12	101.96±15.09	0.313
Respiratory rate	22.38±1.97	23.24±2.04	0.645	21.95±1.69	22.74±1.78	0.462
Oxygen saturation, %	98.63±0.93	98.46±1.03	0.334	98.12±0.80	97.91±1.25	0.523

Bpm: beats per minute, values presented as mean ± standard deviation

groups in our study similar to the study by Wheeler et al. (28) Stephen et al. (21) demonstrated a faster onset of sedation with chloral hydrate versus INM. However, Fallah et al. (5) showed a faster onset with INM. These differences in studies can be due to differences in drug dosage or how they were administered. Midazolam by oral or intranasal routes achieves successful sedation in only 50 to 87 percent of patients undergoing CT, with higher efficacy in patients receiving it by the intranasal route (15,16). Primosch and Guelmann (24), suggested that the use of a commercially available atomizer improved patient acceptance of INM administration but did not influence agent efficacy compared to drops administration for 2- to 3-year-old dental patients in an office setting.

Hijazi et al. (29), showed that chloral hydrate (75 mg/kg) compared to midazolam (0.5 mg/kg) had a higher sedation success rate, shorter time to achieve sedation, shorter length of stay in the hospital, and a longer sedation duration. Of course, oral midazolam has been compared in this study. Klein et al. (25), compared the administration of midazolam by 3 routes to facilitate pediatric laceration repair in the ED. They showed that 0.3 mg/kg INM produced superior sedation to identical doses via the buccal and oral routes with respect to time to onset, quality, and efficacy.

The dosages of medications used in this study were based on previous clinical literature and practice (5,7,10,16). Several clinical trials report satisfactory sedation with either of these dosages (5,21,29). Tsze et al. (18), determined the optimal volume of administration of INM sedation with escalating volumes of administration (0.2, 0.5, and 1 mL) during laceration repair in children in an ED. A volume of administration of 0.5 mL was associated with a statistically shorter time to onset of minimal sedation compared with a volume of administration of 1 mL or 0.2 mL, but all 3 volumes of administration produced comparable clinical outcomes. The effectiveness of INM at a dose of 0.5 mg/kg in the conscious sedation of Iranian children was reported in another study (30).

Parents' average satisfaction with the sedative effect of INM in children was 81.25% and with the sedative effect of OCH, it was equal to 83.54%. Stephen et al. (21), and Fallah et al. (5) showed parents to be more satisfied with chloral hydrate ($p<0.01$), while Wood (31) reported a higher score for INM.

In this study, INM and OCH were both found to be safe and effective drugs for sedation in children undergoing CT scan of the brain. No serious side effects were seen in our study groups.

Study Limitations

There are limitations to the study design that may have impacted the outcomes. The limitations of this study were the small number of patients enrolled and the short duration of follow up, further studies are needed to prove the effectiveness and compare the effects of these drugs.

This study was limited by the use of convenience sampling when the research team was available.

Increased nasal secretion due to the crying of the child following the drugs being sprayed into their nostrils could have diluted the effective dose of the delivered midazolam, thereby causing lower absorption rates. Also, it was observed that some of the drug is lost due to coughing, or dripping from the nares. Therefore, it is not possible to definitively determine the volume and dosage of INM that was delivered intranasally.

To make sure enough concealment, the study pharmacist prepared nasal midazolam using the IV dosage form of midazolam for all patients in the INM group. The effective dosage may not be comparable with available commercial intra nasal midazolam.

Conclusion

A dose of 0.3 mg/kg of INM, used for the sedation of those children between the ages of 1 to 8 years old who are to undergo CT imaging of brain, has as good an efficacy and safety profile as 75 mg/kg of OCH. Compared with chloral hydrate, INM showed an earlier recovery. This study demonstrated that INM and OCH are equally effective for pediatric sedation and have comparable parental satisfaction.

Ethics

Ethics Committee Approval: This study was approved by the ethics committee of Isfahan University of Medical Sciences (approval number: IR.MUI.REC.1396.3.516).

Informed Consent: Informed written parental consent was obtained before enrolling children into the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.H., S.M., M.N.E., Concept: F.H., Design: F.H., Data Collection or Processing: F.H., M.N.E., S.M., M.N.E., Analysis or Interpretation: F.H., M.N.E., H.S., Literature Search: F.H., M.N.E., S.M., M.N.E., Writing: F.H., M.N.E.

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Original Article

Knowledge of Primary Care Physicians on Lysosomal Storage Disorders

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ABSTRACT

Aim: Since patients with lysosomal storage disorders (LSDs) often apply to primary care physicians initially, these doctors play a crucial role in the early diagnosis of LSDs. In this study, we aimed to determine the knowledge and awareness of primary care physicians regarding LSDs.

Materials and Methods: We conducted a survey between January 2016 and April 2016 among primary care physicians from various regions of Turkey. Invitation e-mail was randomly sent to the individual e-mail address of each physician for a web-based survey. The questionnaire globally consisted of three sections with a total of 30 questions. In the first part of the survey, demographic characteristics of physicians (age, gender, career information) were recorded. The second section consisted of questions on LSDs for the evaluation of knowledge among physicians. In the third section of survey, questions were about the reasons of insufficient knowledge on LSDs and possible solutions to raise awareness.

Results: A total of 261 primary care physicians [109 females (41.8%), mean age 40.1±8.8 years] were enrolled in the study. The mean working time was 14.9±8.6 years. Among the participants, 75.8% and 88.8% stated that they had never encountered an LSD patient before and never considered LSDs as a differential diagnosis for any patient, respectively. Fifteen percent of physicians stated that they had no idea about the clinical findings and symptoms of LSD. Another 26.2% of the participants stated that LSD is screened during the neonatal screening program in Turkey. Mean "total knowledge score" of the physicians was 13.47±5.85 points [median=15.0 (10.5-18.0)] out of 25. Six (2.3%) primary care physicians had a total score of "0". Only 1 of them scored "25" points.

Conclusion: Knowledge of primary care physicians on LSDs is not satisfactory in Turkey. Undergraduate medical education and postgraduate educations play a key role to raise awareness.

Keywords: Awareness, primary care physicians, lysosomal storage diseases, survey

Introduction

The lysosome is an intracellular organelle essential for the biochemical breakdown of several molecules such as oligosaccharides, glycosaminoglycans, sphingolipids and other lipids. Defects in lysosomal metabolism lead to accumulation of substrates and result in variable symptoms and findings collectively termed as lysosomal storage disorders (LSDs) which consist of over 40 inherited conditions (1). Age of onset, severity of symptoms and course of progression in LSDs vary from person to person due to the genetic defect affecting enzyme activity. These factors, and typically the absence of evidence at birth make the diagnosis difficult. Therefore, patients with LSD are often misdiagnosed

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and may spend years without knowing what they actually suffer from (2). On the other hand, the development and continual improvement of therapies such as hematopoietic stem cell transplantation (HSCT), enzyme replacement therapy (ERT) and substrate reduction therapy (SRT) for select LSDs make early diagnosis important. Therapeutic outcomes with ERT are generally more satisfactory in the early stages of these disorders (3). However, these disorders are usually not well recognized by physicians and diagnoses are often delayed. As most of the LSD patients present their symptoms first to primary care physicians, these doctors have a crucial role in the diagnosis of LSDs, in making appropriate referrals and coordinating other care support (4).

A literature review revealed insufficient data on LSD awareness levels among primary care physicians. Thus, we aimed to plan a study not only to evaluate awareness on LSDs, but also to determine the problems and expectations of primary care physicians regarding the diagnosis as well as the management of these rare disorders.

Materials and Methods

This study was conducted between January 2016 and April 2016. Primary care physicians from various regions of Turkey participated in the study. An invitation e-mail was randomly sent to the individual e-mail address of each participant. Google Forms (Google Inc., CA, USA) was used to create this web-based survey, invitation e-mails and data collection to ensure privacy. No consent was obtained.

The Questionnaire

The questionnaire globally consisted of three sections with a total of 30 questions (Table I). In the first part of the survey, demographic characteristics of physicians (age, gender, career information) were recorded.

The second section consisted of questions on LSDs for the evaluation of knowledge among physicians. For the objective evaluation of the participants, we scored the answers of the 15 questions on LSDs in this part of survey. The first part of the questions was to write down the names of three LSDs (1 point each), the estimated prevalence of LSDs (correct answer was 1 point), the pathogenesis of LSDs

Table I. The questionnaire (English version)

1.	Age	
2.	Gender	M/F
3.	How long have you been working as a medical doctor?	
4.	How long have you been working as a family doctor?	
5.	Which city are you working in?	
6.	Have you worked in any metabolic disease clinic before?	Y/N
7.	Do you know someone with a metabolic disease?	Y/N
8.	If yes, what is the diagnosis?	
9.	What is your level of knowledge regarding lysosomal storage diseases?	1- No idea to, 10- It is my specialty
10.	Where did you learn about lysosomal storage diseases?	*Medical education *During my internship *Preparation for TUS exam *In the clinic *My personal studies *Following national magazines *In congress *I have no information regarding lysosomal storage disease *Other
11.	Do you know any lysosomal storage disease?	Y/N
12.	If yes, can you please write down three of them?	
13.	Have you ever seen a patient with a lysosomal storage disease?	Y/N
14.	Do you believe that there was a patient who might have had a lysosomal storage disease in your past career?	Y/N
15.	What do you think about the incidence rate of lysosomal storage diseases?	
16.	How many lysosomal storage diseases do you think there are?	

Table I. Continued

17.	Which one of the given might be true for the pathogenesis of lysosomal storage diseases?	*Number of lysosomes contained in a cell are high from birth *Decrease in enzymes within lysosomes based on quantity or functionality from birth *Dysfunctionality of lysosomes contained in cells due to aging *No idea *Other
18.	Can genetic mutations cause lysosomal storage diseases?	Y/N
19.	Does consanguineous marriage increase the risk of lysosomal storage diseases?	Y/N/No idea
20.	Is Turkey, one of the countries where lysosomal storage diseases are observed the most?	Y/N
21.	Which one of the given findings can be observed in lysosomal storage disease patients?	*Growth and developmental delay *Mental retardation *Coarse facies *Hepatomegaly *Splenomegaly *Cataract and retinal findings *Bone deformities *Cardiomyopathy *Seizure *Abnormal renal function test *No idea
22.	Can clinical findings of lysosomal storage disease be observed from birth?	Y/N/No idea
23.	Is it possible to prevent sequalae of lysosomal storage disease?	Y/N/No idea
24.	Do any of the lysosomal storage diseases have special treatments?	Y/N/No idea
25.	Does a patient oriented diet have an important role in treating lysosomal storage diseases?	Y/N/No idea
26.	Is there an enzyme replacement treatment approach in lysosomal storage diseases?	Y/N/No idea
27.	Is there any lysosomal storage disease included in the newborn screening program in Turkey?	Y/N/No idea
28.	Given some patients with diagnosed lysosomal storage diseases. After scanning these patients, would you reconsider your previous patients with lysosomal storage diseases? Male 25 with Isolated splenomegaly and no other findings / Female child 7 with attention deficit and hyperactivity syndrome / Female 40 with isolated left ventricle hypertrophy / Male 28 with isolated proteinuria and kidney tests in norms / Female 42 with stroke attack without hypertension or hyperlipidemia / Female 30 with petechia like angiokeratomas / Female 21 with stomach ache, diarrhea and diagnosed irritable bowel syndrome since puberty	Y/N
29.	Ten cm of splenomegaly is observed on a 16-year-old patient submitting the complaint of nose bleeding. Patient has thrombocytopenia and leukopenia in laboratory findings and bone marrow aspiration shows foam cells. What is the most probable diagnosis for this patient?	
30.	If you think your level of knowledge regarding lysosomal storage diseases is lower than 5, what would be the reason(s)?	*Forgetting knowledge due to the rarity of these diseases *Insufficient undergraduate medical education *Inadequate attention to LSDs in congress *Insufficient literature on LSDs published in Turkish *Other

LSD: Lysosomal storage disorders

(correct answer was 1 point), the role of consanguinity and mutations, and the status of Turkey in the world in terms of the frequency of LSDs (each correct answer was 1 point). In the second part, common clinical findings of patients with LSD (growth and developmental delay, mental retardation, coarse facies, hepatomegaly, splenomegaly, seizure, skeletal abnormalities, cardiomyopathy, renal dysfunction, eye findings, (Table II) were listed in one question and physicians were asked to click on the symptoms that may be seen in LSD patients. This question and the following 6 questions were about clinical findings, symptomatology, diagnosis and treatment modalities of LSDs (in this section, correct answers were equivalent to 16 points in total). In the remaining question, clinical and laboratory findings of a hypothetical adolescent patient with Gaucher's Disease were described and the physicians were asked to write the true possible diagnosis (1 point). The total score of this section was 25 points.

In the third section of this survey, questions were about the reasons of insufficient knowledge on LSDs and possible solutions to raise awareness. The study protocol was designed in compliance with the 1964 Declaration of Helsinki. The study was approved by the Ethics Committee of Dokuz Eylül University Hospital (approval number: 2016/03-14).

Statistical Analysis

Data were recorded with the Statistical Package for Social Sciences version 15.0. Continuous and categorical variables were reported as mean ± standard deviation [median (25-75 percentiles)] and number (%), respectively.

Table II. Knowledge on different clinical findings of LSD patients among primary care physicians (%)

Clinical findings	n (%)
Growth and developmental delay	203 (78.1)
Mental retardation	170 (65.4)
Coarse facies	160 (61.5)
Hepatomegaly	160 (61.5)
Splenomegaly	151 (58.1)
Cataract and retinal findings	139 (53.5)
Bone deformities	136 (52.3)
Cardiomyopathy	118 (45.4)
Seizure	115 (44.2)
Abnormal renal function test	109 (41.9)
No idea	39 (15.0)

LSD: Lysosomal storage disorders

Results

Demographics

A total of 261 primary care physicians [109 females (41.8%), mean age 40.1±8.8 years, median=40.0 (32.0-47.0) years] were enrolled in the study. Ninety-three (35.6%) physicians, 87 (33.3%) physicians and 81 (31.1%) physicians contributed from the western, middle and eastern parts of Turkey respectively. The mean working years as primary care physicians was 14.9±8.6 years [median=15.0 (7.0-22.0) years]. Among the participants, 236 (90.8%) and 197 (75.8%) stated that they had not worked at any metabolic disease center previously and that they had never encountered any patients diagnosed with LSD before, respectively.

Knowledge About LSDs

Among the participants, 87.3% and 37.3% thought that parental consanguinity is a risk factor for LSD and that Turkey is one of the countries where LSDs are frequently seen, respectively. One hundred and forty (55.4%) of them suggested that the symptoms and findings of LSDs are evident at birth. A total of 26.2% of the participants stated that LSD is screened during the neonatal screening program in Turkey. Another 16.5% of them had no idea about the neonatal screening program for LSD in Turkey. In their practice, 231 (88.8%) physicians had never considered LSDs as a differential diagnosis for any patient. Participants were asked to write down the three most commonly known LSDs in the survey. Gaucher's disease, Niemann Pick disease and mucopolysaccharidosis were the most commonly known LSDs.

The mean "total knowledge score" of the physicians was 13.47±5.85 points [median=15.0 (10.5-18.0)]. Six (2.3%) primary care physicians had a total score of "0". Only 1 of them scored "25" points (Table III). There was no correlation between scores and the primary physicians' ages, working years and geographic area where they work. When common clinical findings were listed, 15.0% of the participants stated that they had no idea about the clinical findings and symptoms of LSD (Table II). Most of the

Table III. Total knowledge scores of primary care physicians

Score	Participants (n, %)
0-5	36 (13.7)
6-10	29 (11.1)
11-15	83 (31.8)
16-20	86 (32.9)
21-25	27 (10.3)

participants selected growth and developmental delay, mental retardation and coarse facies as findings of LSD patients. The lowest level of knowledge was observed with cardiomyopathy, seizure and renal abnormalities (Table II). In the last part of this section, participants were asked to make a differential diagnosis for a hypothetical patient with a lysosomal storage disorder. The patient was described as a 16-year-old male with recurrent epistaxis and 10 cm of splenomegaly, together with laboratory investigations showing leukopenia and thrombocytopenia. Bone marrow aspiration of the patient revealed foamy cells and no atypical cells. Based on this information, 60 (23.0%) of the 261 primary care practitioners considered Gaucher's disease for the differential diagnosis.

Primary Care Physicians' Sources of their Knowledge on LSDs and Reasons of İnsufficient Knowledge

Physicians were asked about the main source of their LSD knowledge. A total of 130 physicians (49.8%) stated that they had gained their information about LSDs during their undergraduate education at medical school. On the other hand, 36.4% of physicians declared that they had gained their knowledge on LSDs during their studies for the [Medical Specialty Selection Examination (TUS)], which is conducted after undergraduate medical education in Turkey. Thirteen participants (5.0%) stated that they had obtained their knowledge from academic meetings or papers. Of note, 23 physicians (8.8%) declared that they had no idea about LSDs.

The most commonly specified reasons of insufficient knowledge on LSDs were forgetting relevant information due to the rarity of these disorders, insufficient undergraduate medical education, inadequate attention to LSDs in congress and a lack of papers on this subject published in Turkish (Table IV).

Discussion

The most important finding of this study is the fact that awareness and knowledge level of primary care physicians on LSDs is not satisfactorily sufficient, and undergraduate medical education about LSDs is inadequate. In this study, nearly 90% of the participants had never considered LSDs as a differential diagnosis for any of their patients before. We conducted a scoring system consisting of 15 questions about LSDs for the objective evaluation of participants. In this survey, the mean score was 13.47±5.85 points. Six primary care physicians had a score of "0" and only one physician achieved the maximum score of 25 points. We described a hypothetical patient with Gaucher's disease and only one quarter of physicians established the correct diagnosis. In one study, Bulbul et al. (4) evaluated the awareness of Fabry disease in physicians who were working in the city of Kırıkkale. Consistent with our study results, they determined that only 22% of physicians considered Fabry disease in patients with clinical findings of Fabry disease as a differential diagnosis (4).

Since many patients with LSD present their symptoms first to a primary care physician, these doctors have a crucial role in the diagnosis of LSDs, in making appropriate referrals and coordinating other care support (5). People with rare diseases like LSDs are often referred from one specialist to another, with a list of symptoms and subsequent treatment failures. The National Commission on Orphan Diseases reported that 30% of patients suffering from a rare disease end up waiting up to 5 years to receive a correct diagnosis, 15% take 6 years or more for the correct identification, and 50% reported receiving a correct diagnosis within 1 year of visiting a physician (6). Also, Kishnani et al. (7) revealed that the diagnostic delay was up to 12.6 years for Pompe disease as per the Pompe Registry. Obtaining a detailed family history, carefully documenting the symptoms and signs of presentation, and making an early referral to specialist services would help decrease diagnostic delays and allow earlier intervention (8).

One of the most striking results of this study was the answers about the neonatal period and newborn screening programs. In recent years, one of the most common investigated issues has been newborn screening in LSDs due to the advantages in treatment for some LSDs with ERT, SRT, and HSCT (9-11). LSDs are typically not evident at birth and they are commonly progressive in nature. Both ERT and HSCT are more effective when initiated early during the course of the disease, advocating for newborn screening for these LSDs. There has been a nationwide newborn screening program in place in Turkey since 2007 for phenylketonuria, biotinidase deficiency and

Table IV. Reasons of insufficient knowledge about LSDs declared by primary care physicians

Reasons	n (%)
Forgetting knowledge due to the rarity of these diseases	229 (88.4)
Insufficient undergraduate medical education	116 (44.8)
Inadequate attention to LSDs in congress	61 (23.6)
Insufficient literature on LSDs published in Turkish	19 (7.3)

LSD: Lysergic acid diethylamide

congenital hypothyroidism. Finally, in 2015 cystic fibrosis was added to the newborn screening program. In this study however, 26.2% of primary care physicians stated that LSDs are screened during the neonatal screening program in Turkey, while in fact none of the LSDs have been included in screening yet in our country. Moreover, more than half of primary care physicians suggested that symptoms and findings of LSDs occur at birth. In general, newborn screening is done for disorders which are asymptomatic in the neonatal period, at least during the early postnatal days. Therefore, the relevant explanations were contradictory.

Consistent with the literature, most of the primary care physicians associated their lack of knowledge and awareness on LSDs with insufficient undergraduate medical education and inadequate attention to LSD in congress. Poor rotation at metabolic disease departments and having seen no LSD patients before, as observed in our study, may be explained by insufficient undergraduate medical education. Furthermore, high rates of acquiring knowledge on LSDs during the studies for the TUS among primary care physicians highlights the problems of undergraduate medical educational in Turkey. It is generally unrealistic to expect a rare disease diagnosis to be made during an initial primary care consultation. However, many patients with rare diseases will present their symptoms first to a primary care physician. In terms of reducing the diagnostic gap, all primary care physicians play a crucial role in making appropriate referrals and this is possible only with education. Therefore, the role of undergraduate medical education is essential in providing a good foundation for the future doctors involved in this field (12,13). Raising awareness on the burden of LSDs is possible with increased knowledge regarding the epidemiology and impacts of LSDs as well as by providing educational resources and networking opportunities for primary care physicians (8,14,15).

Conclusion

Knowledge and awareness of primary care physicians on LSDs are not satisfactory in Turkey. However, the relatively low number of participants may be a limitation of our study, and further studies involving a greater number of primary care physicians are warranted to confirm our results. On the other hand, to the best of our knowledge, this is the first study performed to date to investigate the awareness and knowledge status of primary care physicians regarding LSDs. Undergraduate and postgraduate medical training play the key role to increase knowledge, thereby to reduce diagnostic delays and ultimately to improve health outcomes and quality of life for patients. Improved communication between metabolic clinics and primary care physicians, combined with continuing medical education programs may be useful tools to improve the diagnosis of these rare diseases and appropriate patient management.

Ethic

Ethics Committee Approval: The study was approved by the Ethics Committee of Dokuz Eylül University Hospital (approval number: 2016/03-14).

Informed Consent: No consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.A., E.K., S.B., Design: N.A., E.K., S.B., Data Collection or Processing: E.K., Analysis or Interpretation: N.A., E.K., Literature Search: E.K., Writing: E.K..

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Original Article

The Relationship between Psychosocial Development and Liking of Children in Nurses Working in Pediatric Clinics

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ABSTRACT

Aim: This study was conducted to determine the relationship between psychosocial development and liking of children in nurses working in pediatric clinics.

Materials and Methods: This study was conducted as a descriptive and correlational study on 110 nurses working at two hospitals. Data were collected using an information form, the Modified Erikson Psychosocial Stage Inventory, and the Barnett Liking of Children scale. Descriptive statistical tests, Mann-Whitney U test, Kruskal-Wallis test, Pearson correlation and regression analysis and Cronbach's alpha were used in the data analysis stage.

Results: It was found that there was a positive, weak, and significant correlation between the liking of children and the subscales of trust, autonomy, industry, identity, and generativity ($p<0.05$). At the same time, there was a very weak, positive, and significant correlation between the liking of children and the subscales of initiative and ego integrity ($p<0.05$). No significant correlation was observed between the liking of children and the subscale of intimacy ($p>0.05$). It was observed that there was a weak correlation between the level of liking of children and the determinant variables of trust, autonomy, initiative, industry, identity, intimacy, generativity, and ego integrity ($R^2=0.133$).

Conclusion: It was concluded that nurses' levels of trust and autonomy increased the level of liking of children.

Keywords: Child, developmental, love, nursing, pediatrics, psychology

Introduction

According to Erikson, human beings go through eight stages of development throughout their lifetime. Each stage of development has its distinctive developmental goals (1). In every stage, a positive feeling and a negative feeling (such as trust versus mistrust) or an element dissociate and mature. The conflict between these two opposite feelings is the subject of the crisis that is peculiar to that stage. Towards the end of every stage, the dominant feeling becomes obvious (2,3). One of the mostly accepted forms of unrequited love is to like a child. Children are valuable individuals whose all needs are met as best as possible by using the available facilities (4).

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Nurses should know that children have different psychological, physiological, and physical characteristics from adults, an underdeveloped but constantly developing process of comprehension, and different reactions and perceptions towards diseases according to their developmental characteristics and chronological age (5-8). They should also know that care needs to be provided according to the age and development level of the child using both verbal and non-verbal communication methods in accordance with family-centered care (7,8).

A nurse's liking/disliking of children is important in terms of care and communication. The United Nations' Declaration of the Rights of the Child states, "A child needs love and understanding in order to develop her or his own identity fully and compatibly" (5). Therefore, in case of impairment of health during which the child needs love and attention most, it is an important need for her or him to be liked by nurses and other medical personnel. Nursing and especially nursing in pediatric clinics is grounded on the liking of children, empathy, and communication. Nurses' liking of children causes them to accept them more easily, enjoy spending time with them and be more careful and attentive in communication with them (9).

As is seen, there is evidence proving that if nurses who work with the child population have knowledge about children's development levels and like them, this will make a significant contribution to their care. It is important for nurses working in pediatric clinics to know not only children's development levels but also their own development levels in terms of interventions to be performed for children and the care-related approach. Studies conducted in Turkey have reported that nurses working in pediatric clinics have higher levels of liking children (6,10,11). However, when examining the literature, there is no information about the psychosocial development levels of nurses working in pediatric clinics. In the literature, there is no evidence about whether or not development levels of nurses working in pediatric clinics affect their levels of liking children. It is thought that knowing nurses' development levels and levels of liking of children may be effective on the quality of care and formation of scientific evidences. For this reason, this study was conducted to determine nurses' psychosocial development and liking of children and reveal the relationship between these two concepts.

Materials and Methods

Design, Sample and Setting

This study was conducted in a descriptive and correlational design at two hospitals located in İstanbul between February and March 2017. The population of the study consisted of 198 nurses working in pediatric clinics; whereas, the sample consisted of 110 (55.55%) nurses who volunteered to participate in the study. All nurses at the hospitals who agreed to participate in the study were included in the study without making discrimination.

Study Questions

1-What are nurses' scores of psychosocial development?

2-What are nurses' scores of liking of children?

3-What is the relationship between nurses' scores of psychosocial development and scores of liking of children?

4-What is the relationship between nurses' socio-demographic characteristics and scores of psychosocial development?

5-What is the relationship between nurses' socio-demographic characteristics and scores of liking of children?

Instruments

Information Form for Nurses: The information form consisted of a total of 10 questions including four open ones and six closed ones for determining the socio-demographic characteristics of nurses.

The Modified Erikson Psychosocial Stage Inventory (MEPSI): The Erikson Psychosocial Stage Inventory (EPSI) was developed by Rosenthal, Gurney, and Moore in 1981 for the purpose of measuring Erikson's first six stages of development (trust, autonomy, initiative, industry, identity and intimacy). Internal consistency coefficients of the inventory vary between 0.57 and 0.75 (12). In the 80-item Modified Erikson Psychosocial Stage Inventory (MEPSI), which is the modified form of the EPSI and was developed by Darling-Fisher and Leidy (1988) (13); items of the six stages of development in the original inventory were modified and items aimed at measuring the stages of generativity and ego integrity were also added. The inventory was performed on healthy adults. Turkish validity and reliability of the MEPSI was conducted by Ozgungor and Acun Kapikiran (14). The MEPSI consists of a total of 10 items that measure five positive and five negative attitudes corresponding to successful and unsuccessful analyses for each stage. The inventory was developed as a five-point Likert scale consisting of the options from "strongly disagree" to "strongly agree". Reliability coefficients regarding the

subscales of the inventory vary between 0.75 and 0.85 and the reliability coefficient of the overall inventory is 0.97 (13). In this study, the reliability coefficient of the inventory was found to be 0.92.

The Barnett Liking of Children scale: This scale was developed by Barnett and Sinisi (15) in 1990. The Turkish validity and reliability study of the scale was conducted by Duyan and Gelbal (4). The scale includes 14 items and individuals are asked to express their opinions about each item in seven levels varying from "Strongly disagree" to "Strongly agree". Among the items aimed at determining "liking of children", four have a negative meaning (items 3, 6, 10, and 13), whereas ten have a positive meaning. While high scores signify that people like children more, low scores signify that the level of liking of children is low. While the internal consistency coefficient of the Barnett Liking of Children scale was determined as 0.93, the test-retest reliability coefficient was determined as 0.91 (15). In this study, the reliability coefficient of the scale was found to be 0.88.

Data Collection

Data collection tools were applied by the researchers conducting face-to-face interviews with nurses. The nurses who agreed to participate in the study filled in data collection forms independently from other nurses in a quiet and empty room for 15 minutes on average.

Ethics

In order to conduct the study, ethics committee approval from the İstanbul University Social and Human Sciences Ethics Committee (approval number: 2016/157), institutional permission from the hospitals, written consent from the nurses who agreed to participate in the study, and the necessary permission from the scale authors were obtained.

Statistical Analysis

The data obtained in the study were analyzed using the SPSS for Windows 22.0 program. In data assessment, number, percentage, mean, and standard deviation among descriptive statistical methods were used. While quantitative continuous data between two independent groups were compared using the Mann-Whitney U test, quantitative continuous data between more than two independent groups were compared using the Kruskal-Wallis test. Following the Kruskal-Wallis test, the Mann-Whitney U test was used as a supplementary test for determining the differences. Pearson correlation, regression analysis and Cronbach's alpha were applied between continuous variables of the study. The data obtained were evaluated at a confidence interval of 95% and significance level of less than 5%.

Results

Descriptive Characteristics

It was found that 90.9% of the nurses participating in the study were female, 9.1% were male and their average age was 29.47±6.56 (minimum: 20, maximum: 51) years. When examining the educational background of the nurses, it was determined that 14.5% were high school graduates, 15.5% had an associate's degree, 56.4% had a bachelor's degree, and 13.6% had a master's degree. 50.9% of the nurses were married and 31.8% had children.

When examining the durations of the participating nurses working life in pediatric services, it was observed that they had worked for 5.45±5.16 (minimum: 0.08, maximum: 29) years on average and when considering their total duration of working in the profession, it was observed that they had worked for 7.73±6.55 (minimum: 0.83, maximum: 34) years on average. It was determined that the average weekly working hours of the nurses was 49.59±8.92 (minimum: 40, maximum: 80) hours. 49.1% of the nurses who participated in the study were working in intensive care units, 25.5% in internal medicine services, 14.5% in pediatric emergency services, 5.5% in pediatric surgery services and 5.5% in pediatric hematology services. When the nurses were asked about whether or not they liked the profession of nursing, 84.5% of them answered yes and 15.5% answered no.

The Nurses' Psychosocial Development Levels and Levels of Liking of Children

It was determined that while the nurses participating in the study had moderate levels of trust, they had very high levels of autonomy, initiative, industry, identity, intimacy, generativity, ego integrity and very high levels of liking of children (Table I).

Comparing the Nurses' Psychosocial Development Levels and Descriptive Characteristics

There was no significant difference between the nurses' psychosocial development levels and age ($p>0.05$). When examining nurses' psychosocial development levels based on their educational background, it was found that the nurses who were high school graduates had statistically significantly lower levels of trust and autonomy than those nurses with associate degrees, bachelor's degrees or master's degrees ($p=0.02$, $p=0.01$).

When examining the correlation between nurses' psychosocial development levels and duration of working in pediatric services, it was determined that the nurses who had worked in pediatric services for more than a year had significantly higher levels of trust (p=0.01), identity (p=0.01), autonomy (p=0.02), and generativity (p=0.03) subscales than nurses who had worked in pediatric services for less than a year. It was determined that the those nurses whose total duration of working in the profession was 6-10 years had higher scores of intimacy (3.875±0.453) than those nurses whose total duration of working in the profession was 5 years and below (3.593±0.416). When examining nurses' psychosocial development levels according to weekly working hours, it was determined that those nurses who worked for 60 hours and above had statistically significantly lower scores in the subscale of trust than those nurses who had worked for 40-59 hours a week (p=0.00).

When examining whether or not the nurses' psychosocial development levels showed a significant difference in terms of the department where they worked, it was determined that those nurses working in intensive care units had higher scores in the subscale of trust than the nurses working in other departments (p=0.01), and those nurses working in intensive care units and pediatric emergency departments had higher scores in the subscale of ego integrity than nurses working in the other departments (p=0.03).

When examining the nurses' psychosocial development levels based on their state of liking their profession; it was found that those nurses who stated that they liked their profession had significantly higher mean scores in the subscales of trust (p=0.00), initiative (p=0.04), intimacy (p=0.00), and ego integrity (p=0.00) when compared to those nurses who stated that they did not like their profession. Married nurses had lower scores of initiative compared to single nurses (p=0.02). The nurses who had children had lower scores of initiative than the nurses who had no children (p=0.01).

Table I. Modified Erikson Psychosocial Stage Inventory and Liking of Children Levels (n=110)

MEPSI	Mean	SD	Minimum	Maximum
Trust	3.360	0.541	1.800	4.500
Autonomy	3.839	0.405	2.900	4.800
Initiative	3.896	0.412	2.900	5.000
Industry	4.067	0.453	3.100	5.000
Identity	3.906	0.432	2.700	5.000
Intimacy	3.701	0.435	2.600	4.600
Generativity	3.721	0.404	2.900	4.700
Ego integrity	3.631	0.469	2.500	4.900
Liking of children	86.555	12.375	41.000	98.000

MEPSI: Modified Erikson Psychosocial Stage Inventory, SD: Standard deviation

Comparing the Nurses' Levels of Liking of Children and Descriptive Characteristics

Table II shows the results of the relationship between the pediatric nurses' liking of children and some socio-demographic characteristics.

The Relationship between the Nurses' Psychosocial Development Levels and Levels of Liking of Children

When comparing the scores obtained by the nurses from the subscales of psychosocial development and the liking of children scale (Table III), it was found that there was a positive, weak, and significant correlation between liking of children and the subscales of trust, autonomy, industry, identity, and generativity ($p<0.05$). Additionally, there was a very weak, positive, and significant correlation between liking of children and the subscales of initiative and ego integrity ($p<0.05$). No significant correlation was observed between liking of children and the subscale of intimacy ($p>0.05$).

Regression analysis, which was conducted to determine the cause-effect relationship between liking of children and the scores obtained by the nurses from the subscales of trust, autonomy, initiative, industry, identity, intimacy, generativity, and ego integrity of MEPSI was found to be statistically significant (F=3.088; p=0.004). It was observed that there was a weak correlation (the explanatory power) between the level of liking of children and the determinant variables of trust, autonomy, initiative, industry, identity, intimacy, generativity, and ego integrity (R^2=0.133). It was determined that nurses' levels of trust (ß=5.632) and autonomy (ß=6.819) increased their levels of liking of children (Table IV).

Discussion

Comparing the Nurses' Psychosocial Development Levels and Descriptive Characteristics

In this study, it was determined that the nurses had moderate scores on the trust subscale and high scores on the other seven subscales in the MEPSI. Erikson believes that the sum of trust which consists of infancy experiences depends not only on the quantity of food given or demonstrations of love, but mainly on the quality of the relationship with their mother (1). In the first year of life, an infant's psychosocial

duty is to learn to trust. The sense of trust arising from the relationship between the mother and infant forms the basis of an infant's future interpersonal relations (16).

In this study, there was no statistically significant difference between the nurses' psychosocial development levels and age. Among nurses who participated in the study; high school graduates had lower scores of trust and autonomy, which are the subscales of psychosocial development, compared to those nurses with associate degrees, bachelor's degrees or master's degrees. It has been reported that at least a bachelor's degree is required in order for nursing to acquire professionalization (17). It may be thought that an increase in educational level affects positively the nurses' levels of trust and autonomy.

Table II. The Relationship between the Nurses' Liking of Children and some socio-demographic characteristics

	Group	**n**	**Mean**	**SD**	**Test value**	**p value**	**Difference**
Age	20-25 (1)	37	80.243	15.016	20.104*	0.000	3>1 4>1 3>2 4>2
	26-30 (2)	32	86.375	11.542			
	31-35 (3)	18	91.778	7.689			
	Over 35 (4)	23	92.870	5.039			
Education	High school (1)	16	82.813	14.833	3.770*	0.287	-
	Associate's degree (2)	17	84.412	14.111			
	Bachelor's degree (3)	62	86.919	12.102			
	Master's degree (4)	15	91.467	6.545			
Durations of working in pediatric services	Less than 1 year (1)	10	84.600	9.442	13.738*	0.003	3>1 4>1 3>2 4>2
	1-5 years (2)	58	83.879	13.321			
	6-10 years (3)	31	89.613	11.899			
	10 years or more (4)	11	93.818	4.535			
Total duration of working in the profession	5 years or less (1)	53	83.019	13.082	15.442*	0.000	2>1 3>1
	6-10 years (2)	32	87.656	12.630			
	10 years or more (3)	25	92.640	7.135			
Weekly working hours	40 hours (1)	27	91.259	6.820	16.051*	0.001	1>3 1>4 2>3 2>4
	41-50 hours (2)	52	88.231	12.264			
	51-60 hours (3)	18	79.556	13.232			
	60 hours or more (4)	13	79.769	14.754			
Working area	Internal medicine services (1)	28	87.321	10.488	13.274*	0.010	1>2 3>2 4>2
	Pediatric emergency services (2)	16	80.625	10.905			
	Intensive care units (3)	54	88.500	12.661			
	Pediatric surgery services (4)	6	91.833	7.055			
	Pediatric hematology services (5)	6	76.000	17.754	-	-	-
Whether or not liked the profession	Yes	93	88.054	10.863	482.500**	0.011	-
	No	17	78.353	16.740			
Marital status	Married	56	91.018	7.721	841.000**	0.000	-
	Single	54	81.926	14.499			
Having children	Yes	35	91.600	7.441	820.500**	0.002	-
	No	75	84.200	13.509			

*KW, **MW
SD: Standard deviation

In this study, it was found that those nurses who had worked in the pediatric services for more than one year had higher scores of trust, autonomy, identity and generativity subscales than those nurses who had worked for less than one year. In addition, it was determined that those nurses who had worked in the profession for six years or more had significantly higher scores on the intimacy subscale than those nurses who had worked for five years or less. It is thought that this result is compatible with the study which reports that as the year of experience in nursing increases, professionalism and critical thinking power increase (18).

In this study, it was determined that those nurses in pediatric clinics who worked for 60 hours or more per week had statistically significant lower scores in the subscale of trust. According to the regulations, the weekly working hour of nurses in Turkey is required to be 40 hours (19). Since long-duration working causes nurses to experience attention deficit and fatigue and consequently have a higher risk of making mistakes, the ideation of creating an inappropriate environment for the patients they provide care for and their own security might have affected the subscale of trust in the MEPSI.

In this study, it was determined that those nurses working in intensive care units had higher scores on the trust subscale than those nurses working in the other departments (internal medicine, pediatric emergency department, pediatric surgery, and hematology) and those nurses working in intensive care units and emergency departments also had higher scores on the ego integrity subscale. Nurses working in intensive care units have an important position in shaping the future of safe and quality care. Ambitious and professional nurses who are organized in these units are able to provide a top-level health care service (20). This condition increases the trust of nurses in both themselves and their circle. In addition, nurses encountering complex cases and having the ability to provide a high level of care to these cases increases their accumulation of knowledge and allows them to have higher autonomy than those nurses who work in the other clinics. It may be thought that such factors have a positive effect on these nurses' scores of trust and ego integrity.

In this study, those nurses who liked their profession had statistically significantly higher scores of trust, initiative, intimacy, and ego integrity subscales than those who stated that they did not like their profession. Married nurses had significantly lower scores on the initiative subscale than single nurses. In addition, those nurses who had children had statistically significantly lower scores on the initiative subscale than those nurses who had no children. Karamanoglu et al. (21), reported that nurses who liked their profession had higher professional attitudes than those who did not. When nurses perform their duties professionally and willingly, their levels of trust, initiative, intimacy, and ego integrity are affected

Table III. The Relationship between the Nurses' Psychosocial Development Levels and Levels of Liking of Children

	Psychosocial development subscales (MEPSI)								
		Trust	**Autonomy**	**Initiative**	**Industry**	**Identity**	**Intimacy**	**Generativity**	**Ego integrity**
Liking of children	r	0.341	0.332	0.198	0.340	0.272	0.181	0.266	0.246
	p value	0.000	0.000	0.038	0.000	0.004	0.059	0.005	0.010

MEPSI: Modified Erikson Psychosocial Stage Inventory

Table IV. The effect of psychosocial development Levels of Nurses on Liking of Children

Dependent variable	**Independent variable**	**ß**	**t**	**p value**	**F**	**Modal (p)**	**R^2**
Liking of Children	Stable	42.607	3.400	0.001	3.088	0.004	0.133
	Trust	5.632	2.362	0.020			
	Autonomy	6.819	2.140	0.035			
	Initiative	-5.907	-1.274	0.206			
	Industry	4.500	1.079	0.283			
	Identity	1.065	0.261	0.795			
	Intimacy	-1.886	-0.582	0.562			
	Generativity	-0.953	-0.234	0.816			
	Ego integrity	2.378	0.724	0.471			

positively. Those nurses who are married and have children have responsibilities towards their spouse and children at home. Thus, they may have lower levels of initiative than the other group.

Comparing the Nurses' Levels of Liking of Children and Descriptive Characteristics

Every child needs love in order to acquire the basic sense of trust and develop her or his personality fully and compatibly. On the other hand, hospitalization may disrupt this situation. Especially hospitalized children may perceive their condition as a punishment and think that they are liked less. There is an important need for them to be liked especially by nurses in pediatric clinics who are the primary caregivers in cases of disease and hospitalization (5). It is significant for nurses in pediatric clinics to have the characteristics of liking children, communicating with children, interacting with children and showing patience, concern, flexibility, kindness and tranquility (11).

In a previous study, the nurses' mean score of liking of children was found to be 82.07±16.35 (6). In another study, this mean score was observed to be 82.81±13.00 (10). In yet another study, the value was indicated to be 84.35±13.29 (11). In this study, the mean score was determined to be 86.55±12.37. According to the results of these studies conducted in Turkey, it can be seen that nurses have high levels of liking of children. In addition, it may be considered that nurses who like children prefer to work with children.

When examining the literature (6,10,11); no significant correlation between the score of liking of children and age was reported. In this study, on the other hand, it was concluded that nurses who were older than 31 had higher scores of liking of children than nurses from the other age groups. As a nurse's age increases, their views on events and levels of enduring, tolerating or bearing events may increase. It can be considered that the increase of clinical experience in parallel with increasing age may increase their communication with children and pave the way for liking them more. When nurses' educational background and scores of liking of children were examined, no significant correlation was observed between the variables, which shows a parallelism with the literature (6,10). It may be considered that nurses like children independently from their educational background.

The Relationship between the Nurses' Psychosocial Development Levels and Levels of Liking of Children

In this study, it was concluded that there were positive weak correlations between the nurses' scores of liking of children and their scores of trust, autonomy, industry, identity, and generativity subscales of psychosocial development and a very weak positive correlation between their scores of liking of children and the subscales of initiative and ego integrity; however, there was no significant correlation between their scores of liking of children and the subscale of intimacy. It was determined that the nurses' liking of children had a weak correlation with eight of the subscales of the MEPSI. It was found that the trust and autonomy subscales of the MEPSI increased with the level of liking of children.

Study Limitations

The sample of this study is limited to nurses working in pediatric clinics of only two hospitals included in the study. Examining the forms used as data collection tool only based on the statements of the sample group is another limitation. However, the strength of the study is that the validity and reliability studies of the scales used in the study were conducted.

Conclusion

It was determined that the nurses had high psychosocial development levels except for the subscale of trust, very high levels of liking of children, there was a weak but positive correlation between psychosocial development and liking of children except for the subscale of intimacy and the levels of trust and autonomy, which are among psychosocial development stages, increased with the level of liking of children. The level of psychosocial development of nurses working in pediatrics clinics will help them to love children more. Increasing the levels of trust and autonomy of nurses working especially in pediatric clinics will contribute to increasing the love of children and offering more loving care. In addition, the branch selection of nurses working in pediatric clinics can make a positive contribution to the quality of nursing care. Determination of the levels of liking of children of nurses who intend to work in the pediatric clinics will also be effective on their major selection.

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Ethics

Ethics Committee Approval: In order to conduct the study, ethics committee approval from the İstanbul University Social and Human Sciences Ethics Committee (approval number: 2016/157).

Informed Consent: Written consent from the nurses who agreed to participate in the study, and the necessary permission from the scale authors were obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.Ç.İ., S.Y., Design: M.Ç.İ., S.Y., Data Collection or Processing: A.İ.Y., G.G., G.K., Analysis or Interpretation: M.Ç.İ., A.İ.Y., G.G., G.K., Literature Search: M.Ç.İ., Writing: M.Ç.İ., S.Y., Z.D.

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Original Article

Sleep Quality in Adolescents in Relation to Age and Sleep-related Habitual and Environmental Factors

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ABSTRACT

Aim: Our objective is to evaluate the sleep quality in adolescents in relation to age and sleep-related habitual and environmental factors.

Materials and Methods: A total of 150 adolescents aged 12-20 years [mean (standard deviation) age: 15.5 (1.9) years; 65.3% were female] were included on a voluntary basis in this cross-sectional questionnaire survey. The questionnaire form included items on subject demographics (age, gender), before sleep activities (tea/coffee consumption, reading, use of social media), presence and of electronic devices (computer, television, cell phone) in the bedroom and presence of roommate, as well as items on Pittsburgh Sleep Quality Index (PSQI).

Results: Usual bedtime between 23.00-24.00 p.m. (38.0%), sleep latency of 15 minutes (38.0%), sleep duration of ≥7 hours (79.0%) and usual wake up time between 6.00-7.00 am (41.7%) were the most commonly identified sleeping patterns. PSQI total scores revealed poor sleep quality (scores ≥5) in 82.0% of participants, while 40.0% of participants rated their sleep quality to be poor. Later bedtime (≥24.00) was more likely in late-adolescents (64.7%) than earlier age groups (p=0.009). Sleep latency >30 minutes, difficulty in breathing and bad dreams during sleep, presence of electronic device in the bedroom and use of social media before sleep and difficulty in performing daily activities were associated with higher likelihood of PSQI-based poor sleep quality (p<0.05 for each).

Conclusion: Our findings revealed poor sleep quality (PSQI scores >5) in 82.0% of adolescents, regardless of adolescence period, and association sleep latency >30 minutes, difficulty in breathing and bad dreams during sleep, presence of electronic device in the bedroom and use of social media near bedtime with higher likelihood PSQI-based poor sleep quality.

Keywords: Adolescence, sleep quality, PSQ, media devices, sleep latency

Introduction

Sleep is an essential component of mental and physical development in children and adolescents (1-4). However, insufficient sleep and disturbed sleep patterns are common in the pediatric age, with a rising prevalence throughout adolescence (2,5-7).

Adolescence is considered a period with considerable alterations in sleep pattern in terms of amount and quality (7-10) in relation to physiological, environmental, social and behavioral changes specific to this life period (10-12). The trend of insufficient and deteriorating sleep and poor sleep hygiene among adolescents is considered a public health concern given the short and long term detrimental health outcomes including poor diet; sedative behavior; obesity; reduced immunity; stunted growth; cognitive impairment, poor academic performance and mental health problems

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such as depression, anxiety and suicidal tendencies and substance abuse (2,13-18).

Hence, assessment of sleep quality is considered important for health and well-being of adolescents given the increased risk of alterations in sleep patterns and detrimental sleep hygiene in this period as a potential indicator of poor physical and mental health status (8-10, 18,19).

This study was therefore designed to evaluate the sleep quality in adolescents in relation to age and sleep-related habitual and environmental factors.

Materials and Methods

Study Population

A total of 150 adolescents aged 12-20 years [mean (standard deviation (SD) age: 15.5 (1.9) years; 65.3% were female] were included on a voluntary basis in this cross-sectional questionnaire survey conducted at a tertiary care auditory assessment adolescence center between March 2016 and May 2016.

Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study which was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by the University of Health Sciences, İzmir Tepecik Training and Research Hospital Ethics Committee (approval number: 19/10, date: 15.03.2016).

Study Parameters

Data on patient demographics, sleep-related habitual and environmental factors and sleep quality scores were recorded in each subject using a questionnaire form applied via face-to-face method.

Questionnaire From

The questionnaire form included items on subject demographics (age, gender), before sleep activities (tea/coffee consumption, reading, use of social media), presence and of electronic devices [computer, television (TV), cell phone] in the bedroom and presence of roommate, as well as items on Pittsburgh Sleep Quality Index (PSQI).

Pittsburgh Sleep Quality Index

The PSQI was developed by Buysse et al. (20) as a self-rated questionnaire which assesses several dimensions of sleep quality over a one-month time period. Turkish validation of PSQI was performed by Agargun et al. (21). The scale consists of 18 items, that yield seven component scores including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications and daytime dysfunction. Each component is scored between 0 and 3 and the sum of the component scores yields a global score (range= 0-21) that reflects the composite severity of sleep disturbance. Higher scores indicate a lower quality of sleep. A total score under 5 indicates "good sleep quality", while a score above 5 shows "poor sleep quality".

Statistical Analysis

Statistical analysis was made using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY). Chi-square (χ^2) test was used for the comparison of categorical data. Data were expressed as mean (SD) and n (%) where appropriate. $P<0.05$ was considered statistically significant.

Results

Patient Characteristics and Sleep Patterns

Most of participants (60.0%) were in the late-adolescence period. Usual bedtime between 23.00-24.00 p.m. (38.0%), sleep latency of 15 minutes (38.0%), sleep duration of ≥7 hours (79.0%) and usual wake up time between 6.00-7.00 a.m. (41.7%) were the most commonly identified sleeping patterns (Table I).

PSQI total scores revealed poor sleep quality (scores ≥5) in 82.0% of participants, while 40.0% of participants rated their sleep quality to be poor. Habitual sleep efficiency was ≥85% in 61.3% of subjects (Table I).

Pain and bad dreams during sleep were evident in 34.0% and 68.0% of subjects respectively. Before sleep activities comprised tea/coffee consumption in 36.0% of subjects, reading in 46.0% and use of social media in 48.0%. Presence of roommate and electronic devices in the bedroom was identified in 42.0% and 47.3% of subjects, respectively, while 54.7% of subjects identified to have difficulty in performing daily activities, 42.0% to have difficulty in breathing and 66.7% to wake up in the middle of the night or early morning (Table I).

Sleep Characteristics According to Age Groups

No significant difference was noted in gender distribution, sleep duration, self-rated sleep quality and PSQI sleep quality between early, mid- and late-adolescence groups. Later bedtime (≥24.00) was more likely in late-adolescents (64.7%) than earlier age groups (p=0.009) (Table II).

Factors Associated with Poor Sleep Quality

Sleep latency >30 minutes, difficulty in breathing and bad dreams during sleep and difficulty in performing daily

Table I. Patient characteristics and sleep patterns (n=150)	
Age (year), mean (SD)	15.5 (1.9)
Age group, n (%)	
Early-adolescence (12-14 y)	43 (28.7)
Mid-adolescence (15-17 y)	90 (60.0)
Late-adolescence (18-20 y)	17 (11.3)
Gender, n (%)	
Female	98 (65.3)
Male	52 (34.7)
Sleep duration, n (%)	
≥7 h	119 (79.0)
6-7 h	23 (15.0)
5-6 h	6 (4.0)
<5 h	2 (1.0)
Usual bedtime, n (%)	
≤22.00	30 (20.0)
22.00-23.00	19 (12.7)
23.00-24.00	57 (38.0)
≥24.00	44 (29.3)
Sleep latency, n (%)	
0-15 minimum	57 (38.0)
15-30 minimum	31 (20.7)
31-60 minimum	34 (22.7)
>60 minimum	28 (18.7)
Usual wake up time, n (%)	
<6.00 am	18 (12.0)
6.00-7.00 am	61 (41.7)
07.00-08.00 am	41 (27.3)
08.00-09.00 am	11 (7.3)
>9.00 am	19 (12.7)
Self-rated sleep quality (last month), n (%)	
Very good (0)	24 (16.0)
Fairly good (1)	66 (44.0)
Fairly bad (2)	47 (31.3)
Very bad (3)	13 (8.7)
Habitual sleep efficiency, n (%)[a]	
≥85%	92 (61.3)
75-84%	36 (24.0)
65-74%	14 (9.3)
<65%	8 (5.3)
PSQI total score, n (%)	
Good (<5)	27 (18.0)
Poor (≥5)	123 (82.0)
Before sleep activities, n (%)	
Tea/coffee consumption – Yes	54 (36.0)
Tea/coffee consumption – No	96 (64.0)
Reading – Yes	69 (46.0)
Reading – No	45 (30.0)
Use of social media – Yes	72 (48.0)
Use of social media – No	78 (52.0)
Electronic device in the bedroom, n (%)	
Present	71 (47.3)
Absent	79 (52.7)
Roommate, n (%)	
Yes	63 (42.0)
No	87 (58.0)
Difficulty in performing daily activities, n (%)	
Yes	82 (54.7)
No	68 (45.3)
Difficulty in breathing, n (%)	
Yes	63 (42.0)
No	87 (58.0)
Pain during sleep, n (%)	
Yes	51 (34.0)
No	99 (66.0)
Bad dreams, n (%)	
Yes	102 (68.0)
No	48 (32.0)
Waking up in the middle of the night or early morning, n (%)	
Yes	100 (66.7)
No	50 (33.3)

[a](total # of hours asleep)/(total # of hours in bed) x100
SD: Standard deviation, PSQI: Pittsburgh Sleep Quality Index

activities were associated with higher likelihood of poor sleep quality in terms of both self-rated and PSQI-based scores (Table III).

Experience of pain during sleep and tea/coffee consumption before sleep were associated higher likelihood of self-rated poor sleep quality, while waking up in the middle of the night or early morning, presence of electronic device in the bedroom and use of social media before sleep

were associated with higher likelihood PSQI-based poor sleep quality (Table III).

Discussion

Our findings revealed poor sleep quality (PSQI scores >5) in 82.0% of adolescents, regardless of adolescence period, while 40.0% of adolescents self-rated their sleep quality to be poor. Sleep latency >30 minutes, difficulty in breathing and bad dreams during sleep and difficulty in performing daily activities were highly prevalent in our cohort, which seems to be in accordance with their association with poorer sleep quality based on both self-rated and PSQI-based scores. Presence of electronic device in the bedroom and use of social media near bedtime were also associated with higher likelihood PSQI-based poor sleep quality.

Our findings support the high prevalence of altered sleep patterns in adolescents including poor sleep quality rates of 60-80% based on subjective assessment methods including PSQI, and negative self-perception of sleep quality with self-rated poor quality by nearly half of adolescents (2,11,19,22). Hence, increase in awareness of the problem seems crucial given the consistently reported trend of insufficient and deteriorating sleep among adolescents along with somatic and psychological adverse impacts on health (3,4,23).

Sleep duration (≥7 h in 79.0%) of adolescents in our cohort is consistent with the recommended need for at least 8-10 hours of sleep per night by adolescents (24), while together with usual bedtime (after 23.00 o'clock in 67.3%) and wake up time (6.00-7.00 a.m. in 41.7%) data, sleep patterns in our cohort of adolescents fit in line with previous studies in adolescents (mean age of: 15.2 to 16.4 years) that reported an average bedtime of 23.30-24.00 o'clock, sleep duration of 7.0 to 8.1 hours and wakeup time of 6.75-7.55 o'clock (19,25,26).

Our findings revealed no significant difference between early, mid- and late-adolescence in terms of sleep duration,

Table II. Sleep characteristics according to age groups

	Adolescence period			
	12-14 y (n=43)	**15-17 y (n=90)**	**18-20 y (n=17)**	**p value**
Gender, n (%)				
Female	31 (72.1)	53 (58.9)	14 (82.4)	>0.05
Male	12 (27.9)	37 (41.1)	3 (17.6)	
Sleep duration, n (%)				
≥7 h	36 (83.8)	69 (76.0)	14 (82.0)	0.220
6-7 h	6 (13.9)	16 (17.0)	1 (5.0)	
5-6 h	0 (0.0)	5 (5.0)	1 (5.0)	
<5 h	1 (5.0)	0 (0.0)	1 (5.0)	
Bedtime, n (%)				
≤22.00	11 (25.6)	18 (20)	1 (5.9)	**0.009**
22.00-23.00	5 (11.6)	13 (14.4)	1 (5.9)	
23.00-24.00	12 (27.9)	41 (45.6)	4 (23.5)	
≥24.00	15 (34.9)	18 (20.0)	11 (64.7)	
Self-rated sleep quality, n (%)				
Very good (0)	5 (11.6)	16 (17.7)	3 (17.6)	0.550
Fairly good (1)	17 (39.5)	44 (48.8)	5 (29.4)	
Fairly bad (2)	17 (39.5)	23 (25.5)	7 (41.1)	
Very bad (3)	4 (9.0)	7 (7.0)	2 (7.0)	
PSQI total score				
Good (<5)	7 (16.2)	18 (20.0)	2 (11.8)	>0.05
Poor (≥5)	36 (83.7)	72 (80.0)	15 (88.2)	

PSQI: Pittsburgh Sleep Quality Index

self-rated sleep quality and PSQI sleep quality scores, while late-adolescence was associated with higher likelihood of later bedtimes (after 24.00 o'clock). Similarly, a trend towards later bed times with overall 1 h per night reduction in sleep duration has been reported in late-adolescence, while lack of parent supervision, variability of sleeping hours and more frequent after-school activities are considered amongst the factors contributing to this delay (7,27-29).

In addition, certain factors such as electronic media device use, early school start times and increasing caffeine consumption have also been considered to contribute substantially to the trend of poor sleep quality among adolescents (2,6).

Notably, in our cohort, half of adolescents confirmed to have an electronic device (computer, TV, cell phone) in the bedroom and to use social media before sleep, both of which were also determined to be associated with poorer PSQI scores. This supports the high frequency of having at least one media device in the sleeping environment in the adolescence period, and increased odds of poor sleep quality with presence of media devices (even without use) in the bedroom (2,22,30).

Specifically, presence of electronic devices in the bedroom was reported to be associated with increased likelihood of prolongation of sleep latency, shortening of sleep duration, abnormal catch-up sleep and worse health related quality of life among adolescents (6,18,19,31).

Table III. Factors associated with poor sleep quality

	Poor sleep quality	
	Self-rated	**PSQI-based**
Risk factors	**p value**	**p value**
Sleep latency >30 minutes	**<0.05**	**<0.05**
Difficulty in breathing	**<0.05**	**<0.05**
Bad dreams	**<0.05**	**<0.05**
Difficulty in performing daily activities	**<0.05**	**<0.05**
Pain	**<0.05**	>0.05
Tea/coffee consumption before sleep	**<0.05**	>0.05
Electronic device in the sleeping room	>0.05	**<0.05**
Use of social media before sleep	>0.05	**<0.05**
Waking up in the middle of the night or early morning	>0.05	**<0.05**
Reading before sleep	>0.05	>0.05

PSQI: Pittsburgh Sleep Quality Index

Authors also noted the consistency for adverse sleep outcomes related to access to media devices on weekdays and weekends (18), while an increase in magnitude of the adverse impact has been suggested with use of screen-based media devices in the dark owing to potential role of disrupted circadian rhythms and diminished melatonin secretion (18,32).

Indeed, given the rising access to and use of screen-based media devices, increased awareness of parents, teachers, health professionals and adolescents about the associated adverse sleep outcomes is considered crucial (2,18,19). Accordingly, training and intervention studies targeting sleep hygiene promotion in this group are recommended to improve sleep patterns, cognitive function and educational attainment (2,18,19). In fact, a recent pilot cluster-randomized study has addressed the impact of brief school-based psycho-educative intervention on increase in sleep duration by decreasing electronic media use at night and caffeine consumption in adolescents (33). However, authors noted that the intervention was associated with a significant but modest decrease in electronic media use, but showed no effect on sleep duration, sleep quality, daytime tiredness, and mental wellbeing (33).

Overall, sleep latency was >30 minutes in 41.4% of adolescents in our cohort, while prolonged sleep latency was associated with higher likelihood of self-rated and PSQI-based poorer sleep quality. This seems notable given the 20-26% prevalence of sleep latency of >30 min reported among adolescents and the association of prolonged sleep latency with poorer sleep quality (34). Habitual sleep efficiency was ≥85% in 61.3% of subjects in our cohort, which seems also lower than previously reported rates (83.3%) for ≥85% habitual sleep efficiency in Turkish adolescents (35).

Moreover, difficulty in performing daily activities was highly prevalent in our cohort, while it was also associated with poorer sleep quality scores. This seems in accordance with data from a past study among adolescents indicating significant role of poorer sleep quality on increased likelihood of more negative and less positive affect the next day, along with the predictive role of higher levels of negative and lower levels of positive affect the day before in poorer sleep quality (36). The association of lack of sleep with tiredness, attention deficit, low school performance and difficulty in performing daily activities was also reported in other studies (37,38). Accordingly, strategies on improving sleep quality and daily mood are considered to be useful in terms of adolescent well-being (36).

Study Limitations

Certain limitations to this study should be considered. First, the cross-sectional nature of the study and the relatively small sample size precluded the possibility of drawing extensive causal conclusions. Secondly, our subjects may not represent the general adolescence population due to the recruitment of subjects from a single auditory assessment adolescence center. Third, given the likelihood difference in sleep patterns on weekdays and weekends, lack of data on weekend sleep patterns is another limitation which otherwise would extend the knowledge achieved in the current study.

Conclusion

Our findings revealed poor sleep quality (PSQI scores >5) in 82.0% of adolescents, regardless of adolescence period, and association sleep latency >30 minutes, difficulty in breathing and bad dreams during sleep, presence of electronic device in the bedroom and use of social media near bedtime with higher likelihood PSQI-based poor sleep quality. Future larger scale longitudinal studies in different periods of adolescence are needed to better identify determinants of poor sleep quality, while awareness raising activities for the importance and correlates of sleep quality among adolescents seems crucial for parents, teachers, health professionals and adolescents to improve sleep hygiene and to minimize potential detrimental consequences of poor sleep quality on psychosomatic health, cognitive function and educational attainment among adolescents.

Ethics

Ethics Committee Approval: This study approved by the University of Health Sciences, İzmir Tepecik Training and Research Hospital Ethics Committee (approval number: 19/10, date: 15.03.2016).

Informed Consent: Written informed consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Y.Ş., N.T., Concept: Y.Ş., N.T., Design: Y.Ş., N.T., Data Collection or Processing: Y.Ş., N.T., Analysis or Interpretation: Y.Ş., N.T., Literature Search: Y.Ş., N.T., Writing: Y.Ş., N.T.

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Original Article

Progression of Disease and Viral Agents in Infants Hospitalized for Lower Respiratory Tract Infections

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ABSTRACT

Aim: Acute viral respiratory tract infection is the leading cause of hospitalization for infants and young children in developed countries and is a major cause of death in developing countries. The aim of this study was to identify the viruses in children hospitalized for lower respiratory tract infections (LRTI) during the winter period and to evaluate the relationship between the clinical features of these patients and the severity of their disease.

Materials and Methods: The nasopharyngeal aspirates of 200 patients aged 0-24 months hospitalized with a diagnosis of LRTI were analyzed using the real-time polymerase chain reaction method. We looked for associations between the viral agent, duration of hospitalization and respiratory distress scale.

Results: The viral factor was identified in 150 (75%) patients. Rhinovirus was the most frequent viral agent followed by respiratory syncytial virus and adenovirus; (52.67%), (16.0%) and (8.67%) respectively. The average length of hospitalization for respiratory syncytial virus (p=0.001), adenovirus (p=0.009), influenza A virus (p=0.007), and bocavirus (p=0.009) infections were significantly longer. Adenovirus (p=0.029), respiratory syncytial virus (p=0.001) and bocavirus (p=0.009) were significantly associated with length of hospitalization. No significant correlation was identified between the viruses and respiratory distress scores (p>0.05).

Conclusion: We conclude that in hospitalized children with LRTIs, rhinovirus was the most frequently observed viral etiological agent. A longer period of hospitalization was needed for respiratory syncytial virus, adenovirus and bocavirus in infants with LRTIs. Infants with respiratory infections should be monitored due to the risk of developing severe complications during disease progression.

Keywords: Infant, rhinovirus, respiratory syncytial virus, adenovirus, respiratory tract infections, hospitalization

Introduction

Lower respiratory tract infections (LRTI) are the most common cause of mortality and morbidity among children around the world (1). Acute respiratory tract infection is one of the main reasons for the hospitalization in the young age group, especially in developing countries. Respiratory viruses play a significant role in LRTI in children under the age of one year (2,3). Most viruses spread via droplets and cause infection primarily in the epithelium of the respiratory tract. Simple RTI such as bronchiolitis may cause respiratory failure, especially in children, by initiating severe diseases such as chronic respiratory disorders, and triggering acute asthma attacks (4). Adenovirus,

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coronavirus, and rhinovirus cause endemic infections whereas influenza, parainfluenza virus (PIV), and respiratory syncytial virus (RSV) generally cause epidemics. In addition to the known factors, many studies have been conducted on viral factors and epidemiological information to identify the next generation of respiratory viruses such as human metapneumovirus, coronavirus and bocavirus, which have caused acute respiratory failure recently (5). LRTIs related to viruses create a significant load even in developed countries. Nevertheless, mortality and morbidity are significantly higher in developing countries than developed countries (6). Clinical findings and epidemiological features may vary in different geographical areas (7). In Turkey, there have been only a limited number of studies concerning viral etiology in LRTI. In this study, we aimed to identify the viruses in children hospitalized with LRTI during the winter period and to evaluate the relationship between the clinical features of these patients and the severity of the disease.

Material and methods

This single-center, prospective study was conducted at the Department of Pediatrics at a general tertiary referral state hospital. The hospital is located is one of the most populated regions of a metropolitan city.

The study protocol was approved by the Research Ethics Committee of Bağcılar Training and Research Hospital (approval number: 2015-425) in accordance with the Declaration of Helsinki. Informed consent was obtained from the parents of all study participants.

Study Population

Children aged 0-24 months who were diagnosed with LRTI and were hospitalized at the department of pediatrics, which contains 40 beds, were eligible for inclusion in our study population. The diagnosis of LRTI was made with regard to the complaints of coughing, fever, and respiratory distress, along with clinical findings such as slight rales and rhonchus, and infiltration findings on the chest radiography.

Those children who had an infection along with LRTI, metabolic or endocrine disease, chronic lung disease, heart disease, growth retardation or a history of premature birth and whose families refused to give informed consent were excluded from the study.

There were 300 patients aged 0-24 months who were hospitalized in the department of pediatrics due to LTRI in the period between November 2015 and April 2016. The families of 23 patients refused to participate in the study, 27 patients did not meet the inclusion criteria and the samples of 50 patients were spoiled during the process, so 200 out of 300 participants (aged between 0 and 2 years) were included in the study.

Lower Respiratory Tract Infections

Both pneumonia and acute viral bronchiolitis are major causes of LRTIs in children. In the literature, there is evidence from a number of studies that the infectious base of both acute pneumonia and acute bronchiolitis in children has a mixed etiology of microorganisms (8). A diagnosis of an LRTI should be considered in any child who has an acute onset of respiratory symptoms, particularly cough, fast breathing or difficulty in breathing. Diagnosis includes clinical evaluation, radiographic evaluation and etiological investigations to distinguish between pneumonia and bronchiolitis. The management of the severity of the disease is based on the determination of the causative organisms where possible and necessary. Chest radiographs are taken in all of these patients to confirm the presence of pneumonia and detect complications such as a lung abscess or empyema.

Severity of the Disease

The severity of the disease was evaluated using the respiratory distress scale designed by Bezerra et al. (9) and the patients were evaluated as very mild, mild, moderate, or severe according to the scores of the scale.

Disease severity was assessed at the time of enrolment and categorized as follows:

1. Very mild (upper respiratory tract symptoms/signs only): Upper respiratory tract symptoms are coryza, aching ear, a sore throat and stridor.

2. Mild (lower respiratory tract symptoms/signs +/2 upper respiratory tract symptoms/signs but not needing hospital admission).

3. Moderate (lower respiratory tract symptoms/signs +/2 upper respiratory tract symptoms/signs, needing hospital admission but with oxygen saturations in air 93% on pulse oximetry).

4. Severe (lower respiratory tract symptoms/signs +/2 upper respiratory tract symptoms/signs, needing hospital admission and oxygen with saturations in air 93%).

Lower tract symptoms were classified by the presence of fever, tachypnoea, rhonchi with a respiratory rate as per minute, wheezing, focal or diffuse crackles or decreased vesicular sounds on auscultation and retraction at the end of expiration. Pneumonia was diagnosed according to both clinical or radiologic manifestations in the patient. Cyanosis, dehydration, severe respiratory distress and apnea were diagnosed as severe disease (9,10).

Patients who were in the very mild stage were not hospitalized, mild patients were hospitalized only if they were under 3 months old, moderate and severe patients were hospitalized.

Sample Collection

The nasopharyngeal swab samples of the patients were collected with Vircell branded swabs. The swabs were kept in an appropriate transport medium (HEPES, gelatin, bovine serum albumin, sucrose, and Hank's balanced salt solution including coherent antibiotics) at -80 °C until the study was conducted. The samples were transferred to the Iontech Microbiology Laboratory in accordance with cold chain regulations.

Laboratory Measurements

The RNA/DNA isolation, the reverse transcription of RNA, and Real-time amplification were applied to the samples using the ARVI Screen Real-Time-polymerase chain reaction (PCR) kit (Sacace Biotechnologies S.r.I, Italy).

The RNA samples obtained were studied using a commercial kit (Sacace, ARVI Screen real-TM, hRSV Real-TM, Influenza A, B Real-TM). The cDNA synthesis was performed using a component (Reverta-L) of the kit.

Real-time Polymerase Chain Reaction Analyses

The cDNAs obtained were studied in a Rotor-gene brand (Qiagen) Real-Time-PCR device. Human PIV-1-4 RNA, HKUI human coronavirus RNA, human rhinovirus RNA, human B, C, and E adenovirus DNA, human bocavirus (hBov) DNA and Influenza A, B and hRSV were studied using commercial RT-PCR kits. Positive and negative controls were included in the RT-PCR analysis.

Statistical Analysis

SPSS ver. 23 (IBM Corp. Armonk, NY, USA) statistical package was used for the statistical evaluation. Descriptive statistics are indicated as frequencies and percentages for categorical variables and as means ± standard deviation for continuous variables. In the comparison of the categorical variables, the chi-square test or Fisher's exact probability test were used conditionally. Normal distribution was tested with the Kolmogorov-Smirnov test for continuous variables, while the two-independent-samples t-test was used in the comparison of continuous variables consistent with a normal distribution of two independent groups. Median and Interquartile Range (IQR) values were used for non-normal distributions. The post-hoc power analysis test was used for statistically significant results. Mann-Whitney U test, Kruskal-Wallis tests were used where appropriate. Logistic regression analysis was performed. A p value less than 0.05 was accepted as indicating statistical significance.

Results

A total of 200 patients who were hospitalized with a diagnosis of LRTI and who were eligible according to the criteria mentioned before were included in this study. Viral agents were identified in 150 (75%) of these 200 patients by PCR analyses.

Among these 150 patients, 79 were male (52.67%) and 71 were female (47.33%), and the mean patient age was 7.33±4.72 months.

In 139 patients, only one viral agent was identified. The distribution of the viruses among virus detected subjects was as follows: Rhinovirus in 79 patients (52.67%), RSV in 24 patients (16.0%), adenovirus in 13 patients (8.67%), influenza B virus in 7 patients (4.67%), bocavirus in 6 patients (4.0%), coronavirus in 5 patients (3.33%), and influenza A virus in 5 patients (3.33%).

Moreover, it was observed that certain viruses co-existed in 11 (7.33%) patients. Rhinovirus and RSV co-existed in 8 of these patients, RSV and bocavirus co-existed in 2 patients, and RSV and influenza A virus co-existed in 1 patient. No PIV was detected in any of the patients.

Blood cultures were performed for all patients, the cultures remained negative for any bacterial agents.

The patients presented mostly with coughing as the initial symptom and this was followed by wheezing, high fever, and respiratory distress. The clinical findings of the patients were evaluated by the respiratory distress scale described by Bezerra et al. (9). We observed that 55 patients were mildly distressed, 69 patients were moderately distressed, and 26 patients were severely distressed.

Table I. Relationship between Respiratory Tract Viruses and Respiratory Distress score

There were no differences between the respiratory distress scores of patients when compared in terms of the presence of the various respiratory tract virus (Table I).

Table II. Relationship between Respiratory Tract Viruses and the Length of Hospitalization

The mean duration of hospitalization of the patients was 3.72±3.06 days. When the relationship between the presence of viruses causing LRTI and the duration of hospitalization was evaluated, it was observed that the mean length of hospitalization for patients infected with RSV, adenovirus, influenza A and bocavirus was significantly

longer (p=0.001, p=0.009, p=0.007, p=0.009) respectively (Table II).

Table III. Logistic Regression Analysis of Viral Etiology Associated with Length of Hospitalization

To determine the factors that affected the duration of hospitalization most, logistic regression analysis was performed using viral factors as variables. Adenovirus (p=0.029), RSV (p=0.001) and Bocavirus (p=0.009) were significantly associated with length of hospitalization (Table III).

Patients with co-existing viruses endured longer hospital stays and 2 patients with rhinovirus and RSV and 1 patient with RSV and bocavirus were monitored in the intensive care unit.

Discussion

We identified viral agents in 150 (75%) hospitalized children with LRTI aged 0-2 years. The rate was found to be between 35-90% in studies conducted previously on hospitalized children (11-15). These viruses cause mild to severe disease LRTI. In our study, for those patients in which infections progressed severely, RSV, adenovirus, bocavirus and coronavirus were identified as the viral agents (Table I).

Table I. Relationship between the presence of respiratory tract viruses and respiratory distress score

Respiratory viruses Mild		**Scoring**			**Total, n=150**	**p value**
		Moderate	**Severe**			
Rhinovirus	(+) n	26	38	15	79	0.587
	%	31.0%	50.7%	18.3%	100.0%	
	(-) n	29	31	11	71	
	%	40.8%	43.7%	15.5%	100.0%	
Respiratory syncytial virus	(+) n	6	11	7	24	0.186
	%	25.0%	45.8%	29.2%	100.0%	
	(-) n	49	58	19	126	
	%	38.9%	46.0%	15.1%	100.0%	
Adenovirus	(+) n	3	5	5	13	0.102
	%	23.1%	38.5%	38.5%	100.0%	
	(-) n	52	64	21	137	
	%	38 %	46.7%	15.3%	100.0%	
Influenza B	(+) n	4	2	1	7	0.506
	%	57.1%	28.6%	14.3%	100.0%	
	(-) n	51	67	25	143	
	%	35.7 %	46.9%	17.5%	100.0%	
Bocavirus	(+) n	2	1	3	6	0.08
	%	33.3%	16.7%	50.0%	100.0%	
	(-) n	53	68	23	144	
	%	36.8 %	47.2%	16%	100.0%	
Coronavirus	(+) n	1	2	2	5	0.374
	%	20%	40%	40%	100.0%	
	(-) n	54	67	24	145	
	%	37.2 %	46.2%	16.6%	100.0%	
Influenza A	(+) n	0	4	1	5	0.200
	%	0%	80%	20%	100.0%	
	(-) n	55	65	25	145	
	%	37.9 %	44.8%	17.2%	100.0%	

Similar to other studies, (14-18) the severity of disease increased in patients infected with RSV. Bicer et al. (15) found that pneumonia comorbidity was 43.5% in hospitalized infants infiltrated with RSV. In our study, pneumonia comorbidity with infiltration on chest radiography was 32.3% in children infected with RSV. RSV can be observed during the period from November to July and it reaches its peak during December to May (15).

Adenoviruses are generally observed during the period February to July, reaching a peak during the period April to

Table II. Relationship between respiratory tract viruses and the length of hospitalization

Respiratory tract virus	Length of hospitalization (days)	p value	Post-hoc power	Median	IQR
Rhinovirus					
(+)	3.68±2.84	0.879	-	3	2
(-)	3.76±3.31		-	3	3
RSV					
(+)	6.4±4.28	**0.001**	%99	5	4
(-)	3.28±2.52		-	3	1
Adenovirus					
(+)	5.69±3.8	**0.009**	%69.47	4	6
(-)	3.53±2.93			3	2
Influenza B					
(+)	3.00±2.38	0.448	-	3	2
(-)	3.76±3.10		-	3	2
Bocavirus					
(+)	7.67±4.45	**0.009**	%69.2	7	7
(-)	3.56±2.90		-	3	2
Coronavirus					
(+)	4.60±2.70	0.254	-	3	5
(-)	3.69±3.08		-	3	2
Influenza A					
(+)	6.30±2.70	**0.007**	%63.7	7	5
(-)	3.62±3.04		-	3	2

RSV: Respiratory syncytial virus, IQR: Interquartile range, Post-hoc power analysis test was used for statistically significant results

Table III. Logistic regression analysis of viral etiology associated with length of hospitalization

Viral Agents	B	SE	P	OR	OR 95% CI	
					Lower	Upper
Rhinovirus	-0.008	0.053	0.878	0.992	0.893	1.101
RSV	0.225	0.069	**0.001**	1.253	1.094	1.435
Adenovirus	0.146	0.067	**0.029**	1.157	1.015	1.319
Influenza B	-0.124	0.197	0.527	0.883	0.601	1.298
Bocavirus	0.205	0.078	**0.009**	1.228	1.053	1.431
Coronavirus	0.071	0.111	0.52	1.074	0.864	1.335
Influenza A	0.162	0.085	0.058	1.175	0.995	1.389

OR: Odds ratio, CI: Confidence interval, RSV: Respiratory syncytial virus, SE: Standard error

June and they are reported to progress to severe and fatal (19). In our study, in adenovirus infections, the occurrence of fever and lung infiltration were significantly higher. In our study, adenoviruses had the third highest frequency (9.35%) which is higher than previously reported in other studies conducted in Turkey in hospitalized children, namely 5.6% and 4.8% (12,15). Bezerra et al. (9) also found that adenoviruses were the second most frequent agents in hospitalized patients.

Coronaviruses rarely cause infection during the winter and spring months. In our study, this rate was determined to be 3.59%, which is consistent with other studies. The coronavirus rate was reported as 7.6% by Prill et al. (20) and 1.6% by Lau et al. (21) in hospitalized children between the ages of 6 months and 5 years. It was determined to be 2.9% in another study conducted in Turkey (22).

We observed the ratio of bocavirus to be 4% in our study. In recent years, bocavirus was determined to be between 3% and 21.5%, varying according to the region, in children with acute LRTI (23-25). When we observed the viral agents which caused the longest length of hospitalization RSV, adenovirus and bocavirus were prominent. In a local study, it was found that rhinoviruses were responsible for the longest lengths of hospitalization, after RSV (15). However, in our study, rhinoviruses had less effect on the length of hospitalization. RSV was the second virus to cause long-term hospitalization. For adenovirus, the length of hospitalization was significantly longer and also the respiratory distress score in patients infected with adenovirus varied from moderate to severe. The course of LRTI caused by adenoviruses includes a high and prolonged fever which may cause long hospitalization (19).

Bocavirus caused the longest length of hospitalization, namely 7.67±4.45 days. Moreover, the respiratory distress scores of children infected with bocavirus was severe with infiltration on chest radiography, which is similar to previous studies (26,27). Before the detection method of hBov was developed, children with LRTI were accepted as RSV-negative severe pneumonia patients (28,29). We think that bocavirus infections may be responsible for these cases.

We found rhinovirus to be the most frequent virus (56.83%) followed by RSV (17.26%) and adenoviruses (9.35%). In some studies, the most frequent bronchiolitis agent was observed to be RSV at a rate of 12-60% in hospitalized children under 2 years of age (14-18). In other studies, RSV and rhinovirus were both identified at high rates using the PCR method; 43.6% and 31.8%, respectively, in children admitted to hospital with an acute respiratory infection (30). In a recent study conducted in Thailand, the most common respiratory viruses in hospitalized children with severe pneumonia were determined to be RSV, rhinovirus and adenovirus especially in infants (31).

In the literature, rhinoviruses were found to be responsible for LRTIs and were observed in 14-24% of children hospitalized with bronchiolitis (4,32-35). In the study conducted by Beka et al. (32), the rate of rhinovirus in hospitalized infants under the age of 2 years was 43.7%, while Xie et al. (36) reported 36.2% in children under the age of 1 year. It has been reported that rhinoviruses cause LRTI and bronchiolitis especially in children under 3 years of age (37,38). Rhinoviruses were observed frequently in our study which was performed between November and April, which is the period when rhinoviruses were observed most often as reported by previous studies. The hospitalization in children with LRTI caused by rhinoviruses in infants during the spring and summer months and especially during March and April are reported to be more frequent (34,39). We believe that the number of RSV cases in our study was limited since it was conducted over a period of 6 months.

Although rhinovirus is the most frequent virus we detected, we observed that the respiratory distress score was moderate in 50%, mild in 31% and severe in 18.3% of children infected with rhinovirus. Mild or moderately severe LRTIs caused by rhinovirus were reported in studies (12,14). Also, in the study conducted by Bicer et al. (15) bronchiolitis symptoms related to rhinoviruses were moderate to severe in 29.2% of children.

The rate of bronchiolitis due to influenza A and B was 0.8-12.8% in previous studies and we found the frequency of Influenza A and B to be 4.67% and 3.33% respectively (14,15,18). Influenza A progressed moderately with fever and infiltration in the lungs and caused a long length of hospitalization at 6.30±2.3 days.

We identified multiple factors in 11 samples (7.33%). RSV was the most frequent co-infective virus particularly with rhinoviruses. In one study, 35% of children in the intensive care unit had multiple infections and RSV was the most frequent virus in mixed infections (24.3%) (40). In our study, in the intensive care unit, RSV and rhinovirus co-existed in two out of three patients with severe symptoms and in one patient RSV and bocavirus co-existed. In another study, in 13.8% of children with LRTI, RSV, rhinovirus and hBov were the most frequent and multiple infections were identified similar to our study (41). However, the present viruses may

we detected in the respiratory tract as pathogens, other viruses may be completely asymptomatic in children even if they are present.

One of the strengths of our study is that there are a limited number of studies in our country on the identification of viruses by rapid screening methods in children under the age of 2 years hospitalized with LRTI and this study adds novel information. However, our samples were obtained over a specific time frame, between November and April, not throughout the year and this is the limitation of our study.

Conclusion

In our study, rhinovirus was detected as the most common viral factor in 0-2 years old children who were hospitalized in late winter and early spring due to LRTI, which is different from the common study findings. Rhinovirus was followed by RSV and adenovirus. It appears that RSV and adenovirus play a role in the severity of the disease.

We suggest that infants with respiratory infections should be monitored for the risk of developing severe complications. We think this study will add information to the understanding of viral LRTIs of the infancy period.

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Ethics

Ethics Committee Approval: The study protocol was approved by the Research Ethics Committee of Bağcılar Training and Research Hospital (approval number: 2015-425) in accordance with the Declaration of Helsinki.

Informed Consent: Informed consent was obtained from the parents of all study participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.B.E., M.E., Ö.B.G., Ö.Y., Concept: A.B.E., M.E., Ö.B.G., Design: A.B.E., M.E., Data Collection or Processing: T.D.D., K.Y., Ö.B.G., Analysis or Interpretation: D.K., Ö.B.G., Ö.Y., Literature Search: D.K., T.D.D., K.Y., Ö.Y., Writing: M.E., D.K., A.B.E.

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Original Article

Evaluation of Resistance to Ciprofloxacin and Identification of Mutations in *Topoisomerase* Genes in *Escherichia coli* and *Klebsiella pneumonia* Isolated from Pediatric Urinary Tract Infections

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ABSTRACT

Aim: Urinary tract infection (UTI) is one of the common infectious diseases of children. Due to the limited use of fluoroquinolones in children, they still have no resistance problems as seen in the adult population. However, recent reports suggested an increase in resistance to fluoroquinolones among bacteria causing UTI in children. Therefore, the aim of this study is to evaluate the prevalence of *Escherichia coli* and *Klebsiella pneumoniae* isolates resistant to ciprofloxacin and to detect mutations in their *gyrA* and *parC* genes.

Materials and Methods: The present study is conducted on 78 bacterial strains isolated from children with UTI during 2016-2017 at İmam Reza Hospital in Kermanshah, Iran. The bacteria were identified based on microbiological methods and an antibiotic susceptibility test using disc diffusion and broth microdilution methods. Then, polymerase chain reaction and sequencing were performed to investigate mutations in the *gyrA* and *parC* genes.

Results: Overall, 15.3% of isolates of *E. coli* and *K. pneumonia* were resistant to ciprofloxacin. Sequence analysis confirmed mutations in the *gyrA* and *parC* genes in all of the isolates resistant to ciprofloxacin. The results showed changes in amino acids (ser83leu, ser83phe and Asp87Asn) in codons 83 and 87 in the quinolone resistance-determining regions of the *gyrA* gene, three substitutions in both the 80 and 84 positions in the *parC*, *ser80Ile*, *Glu84val* and *Glu84lys* genes.

Conclusion: The results of this study revealed resistance to ciprofloxacin in the pediatric population. Given that the use of ciprofloxacin in children is limited, this resistance cannot be due to antibiotic selective pressure. On the other hand, the mutations in the *gyrA* and *parC* genes in children was similar to that in adults which indicate that these resistant isolates can be transmitted from adults to children.

Keywords: Urinary tract infections, ciprofloxacin, resistance, fluoroquinolone, *Escherichia coli*, *Klebsiella pneumonia*

Introduction

The urinary tract infections (UTIs) are some of the most important diseases among children. The common UTI pathogens among children are the bacteria in the *Enterobacteriaceae* family, such as *Escherichia coli* and *Klebsiella pneumonia* (1). Despite the fact that beta-lactam antibiotics, cotrimoxazole and ampicillin are the first line of medicine for the experimental treatment of patients with UTI, there are reports of high resistance to these antibiotics

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(2). It is important to select an effective antibiotic in experimental therapy because of the high susceptibility rate, complications and the imposition of treatment costs in pediatric UTIs (3). Although fluoroquinolones are unsuitable for people under the age of 18, due to increased resistance to cephalosporin, these antibiotics can be used to treat of UTIs caused by *E. coli* and multi-drug-resistant Gram-negative bacteria in patients aged 1-17 years (4). Although the use of these antibiotics is limited in children, fluroquinolone resistant strains are abundant. According to previous reports, the resistance to ciprofloxacin in strains of *E. coli* isolated from children with UTI has increased from 1% to 10% and 0.6% to 4% between 2002 and 2009 (5). *E. coli* and *K. pneumonia* are of the most important fluoroquinolones resistant pathogens (6). The topoisomerase II and IV enzymes are involved in bacterial genome replication, and are the main target of fluoroquinolones. The fluoroquinolones, by inhibiting the activity of these enzymes, inhibit the synthesis of bacterial DNA (7). The DNA gyrase consists of two subunits that are coded as gyrA and gyrB. The topoisomerase IV and consists of two subunits encoded by *parC* and *parE* genes. Mechanisms of resistance to quinolones include; 1) mutation in the quinolone resistance-determining region (QRDR) of DNA gyrase and topoisomerase IV, 2) intracellular reduction of the drug due to increased expression of efflux pumps or enhanced cell wall impermeability, and 3) production of *plasmid-mediated quinolone resistance* genes. The main mechanism of resistance is due to mutations in the QRDR region of DNA gyrase and topoisomerase IV. The common location for mutation in *E. coli* and *K. pneumonia* is the *gyrA* gene. Most mutations have been detected in the limited region of QRDR that codes the amino acids 67 to 106. The most common mutations in the *gyrA* gene occur in the nucleotides 248 and 260, which cause changes in the amino acids of ser83 and Asp87; and the most common mutations in the *parC* gene are in the nucleotides 238 and 250, which cause changes in the amino acids of ser80 and Glu84 (8-10). In position 83 of the *gyrA* gene, the amino acid serine is usually replaced by leucine, followed by ser83val and ser83Ala; these alterations increase the Minimum Inhibitory Concentrations (MIC) value of ciprofloxacin. The higher MIC value for ciprofloxacin usually occurs due to mutations in ser83 and Asp87. The frequency of mutations in the QRDR region of gyrA and parC is more common than gyrB and parE. In addition, there is a high level of resistance to fluoroquinolones in isolates with mutations in the QRDR region of parC due to a mutation in gyrA, but the mutations in gyrB and parE have only a complementary role for resistance (7,9). Concerning the resistance to fluoroquinolones, the population of children has not yet encountered the challenges of resistance found in adult populations, but it is important to assess the resistance to fluoroquinolones in children; therefore, this study aimed to evaluate *E. coli* and *K. pneumonia* isolates as the ciprofloxacin-resistant UTI pathogens in children and to detect the mutations in the *gyrA* and *parC* genes and their association with MIC for ciprofloxacin.

Materials and Methods

Bacterial Isolates

This study was performed on all urine specimens of children under 18 years of age who were referred to the İmam Reza Hospital in Kermanshah between 2016 and 2017. The cases were community acquired UTIs. Exclusion criteria were an age of over 17 years, negative urine culture, patients with a colony count less than 10^5 (11). The urine samples were collected by midstream or urine bags. Following this, bacteriological and biochemical tests were used to detect bacteria in all urine specimens (12).

The study was approved by the Kermanshah University Ethics Committee (approval number: 2016/241). All patients were hospitalized in an university hospital and a free and informed consent was obtained from each participatnts.

Antibiotic Susceptibility Testing

The susceptibility of isolates to Ciprofloxacin (5 µg), Imipenem (10 µg), Ampicillin (10 µg), Aztreonam (30 µg), Ceftazidime (30 µg), Cefotaxime (30 µg), Ceftriaxone (20 µg), Gentamicin (30 µg), Tobramycin (10 µg) and Cotrimoxazole (25 µg) (MAST, England) was conducted using a disk diffusion test according to the Clinical and Laboratory Standards Institute (CLSI) guidelines (13). Determination of MIC of Ciprofloxacin (Sigma, USA) was performed by the broth microdilution method according to CLSI criteria (13). The *E. coli* ATCC 25922 strain was used as the control strain. The CLSI breakpoints were used for ciprofloxacin susceptibility (susceptible ≤1 µg/mL; resistant ≥4 µg/mL).

PCR Amplification and Sequencing

Bacterial DNA was extracted using a genomic DNA purification kit (SinaClon, Iran). The QRDR of the *parC* and *gyrA* genes from susceptible and resistant isolates was amplified by PCR using the specific oligonucleotide primers listed in Table I (14,15). The PCR products were detected on 1% agarose gel after electrophoresis, the DNA bands were visualized by GelDoc apparatus (BioRad, USA). All

PCR products for the *parC* and *gyrA* genes were purified with a PCR purification kit and sequenced (SinaColon, Iran). Sequence data were analyzed for homology with genetic data using the National Center for Biotechnology Information GenBank database (http:/www.ncbi.nlm.nih.gov/BLAST/).

Statistical Analysis

All data were analyzed using statistical methods and SPSS version 20. The correlation between mutations and the ciprofloxacin MIC was investigated by Sperman's, Mann-Whitney and Kruskal-Wallis tests. The chi-square test was used to compare resistance of ESBL producing and non-producing isolates. Statistical significance was defined as having a p value less than 0.05.

Results

In this study, 66 isolates of *E. coli* and 12 isolates of *K. pneumonia* of children aged under 18 years were evaluated. The number of girls and boys was 55 (70.5%) and 23 (29.5%), respectively. The age distribution among the 66 (84.6%) patients with *E. coli* infections was as follows; 34 (51.5%) were in the age group of 1-6 years, 8 (12.1%) patients were between 7 and 10 years, 9 (13.6%) patients were in the 11-14 years group while the remaining 15 (22.7%) patients were between 15 and 17 years. The age distribution of the 12 (15.4%) patients with *K. pneumonia* infections was as follows; 10 (83.3%) patients were 1-6 years old, 1 (8.3%) patient was between 7 and 10 years old and 1 (8.3%) was between 15 and 17 years old. The mean age of patients was 6.1±5.59 (maximum of 17 years and minimum of 1 year).

The antibiotic susceptibility pattern to 10 antibiotics and MIC for ciprofloxacin in the 66 isolates of *E. coli* and 12 isolates of *K. pneumoniae* are presented in Table II and Figure 1. The highest antibiotic resistance was observed for ampicillin and cotrimoxazole. *E. coli* strains showed the lowest resistance to Gentamicin, ciprofloxacin and aztreonam while *K. pneumonia* isolates exhibited the least resistance to Tobramycin and ciprofloxacin. No resistance to imipenem was found in either bacteria studied.

Of the 78 isolates, 18 (23.07%) were ESBL producers. Of these 18 isolates, 6 (33.3%) were resistant to ciprofloxacin. Resistance to ciprofloxacin in ESBL-producing isolates was higher than isolates without ESBL (p=0.008) (Table III).

The nucleotide sequence of the QRDR region from gyrA and parC indicated the presence of two mutations in gyrA and two mutations in parC.

DNA sequence analysis of the QRDR of gyrA showed that all isolates of *E. coli* and *K. pneumonia* resistant to ciprofloxacin showed mutations in gyrA at codon 83 and codon 87.

Table I. The primers

Gene	Primer	Target site	Amplicon size (bp)	Reference
parC F *parC* R	5'AGCGCCTTGCGTACATGAAT3' 5'GTGGTAGCGAAGAGGTGGTT3'	QRDR of *parC*	964	(14)
gyrA F *gyrA* R	5'TACACCGGTCAACATTGAGG3' 5'CCGGATCGGTAAGCTTCTTCAAT3'	QRDR of *gyrA*	684	(15)

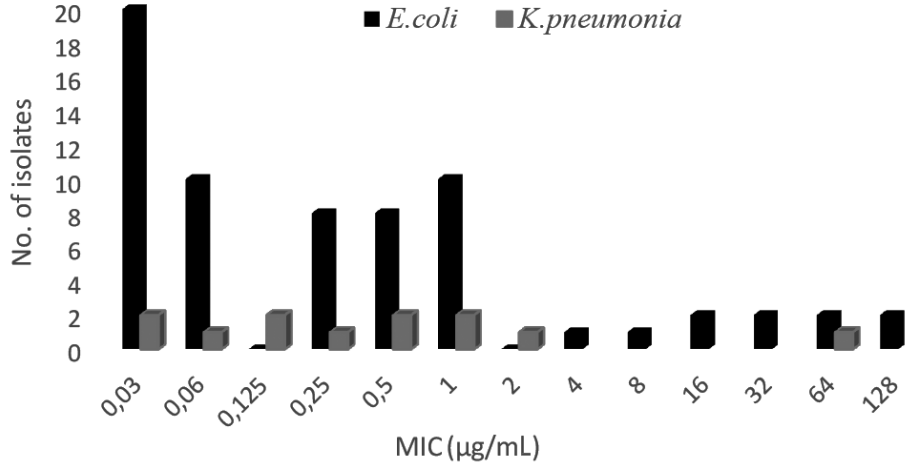

Figure 1. The distribution of isolates according to their Minimum Inhibitory Concentrations level (µg/mL) for ciprofloxacin

The results showed that mutations mapped in the *parC* gene conferring resistance to iprofloxacin were either in the codon Ser80 to Ilu80 or in codon Glut84 to Val 84 for *E. coli* (Table IV). Whereas the *K. pneumoniae* parC mutant conferring resistance to ciprofloxacin was Glut84 to Lysine84 (Table IV).

As shown in Table III, the Ser83 → Leu + Asp87 → Asn mutation in the *gyrA* gene and Ser80 → ILe mutation in the *parC* gene were the most frequent types in those isolates resistant to ciprofloxacin. Curiously, one of the ciprofloxacin sensitive isolate of *E. coli* exhibited a mutation in the *gyrA* gene, but the rest of ciprofloxacin-sensitive *E. coli* and *K. pneumonia* had no mutation in the *gyrA* and *parC* genes (Table V).

The MIC value of ciprofloxacin was higher in those isolates with multiple mutations in the *gyrA* and *parC* genes compared to isolates with a single mutation in the *gyrA* gene or without any mutations in the *gyrA* and *parC* genes (p=0.001).

The nucleotide sequence data of gyrA and parC have been deposited into the GenBank under the accession number of MH425518, MH425519, MH324489, MH324490 and MH523403.

Discussion

In this study, the highest antibiotic resistance was observed for ampicillin and cotrimoxazole. Studies in İran have also reported resistance to ampicillin from 88 to 94% and resistance to cotrimoxazole from 63 to 71% for *E. coli* isolates in pediatric UTIs (2,16,17). It seems that the extensive use of ampicillin and cotrimoxazole as empirical therapy for UTI has resulted in the high resistance of *E. coli* isolates to these antibiotics in İran (18,19). In this and other studies, resistance to imipenem has not been observed in *E. coli* causing UTI; therefore, this drug is still an effective one in the treatment of UTI (18).

In the present study, the prevalence of UTI was higher in girls than in boys, which is consistent with other studies (2,18), due to the structure and anatomy of the female urogenital system (18). Since fluoroquinolones are less commonly used in children, they have not yet encountered the resistance problems occurring in adults (20). Our

Table II. Antibiotic susceptibility of *Escherichia coli* and *Klebsiella pneumonia* isolated from children Urinary tract infections

	***Escherichia coli* (66)**			***Klebsiella pneumonia* (12)**		
Antimicrobial agent	**R**	**I**	**S**	**R**	**I**	**S**
Imipenem	0 (0)	0 (0)	66 (100)	0 (0)		100 (12)
Ampicillin	74.2 (49)	6.1 (4)	19.7 (13)	100 (12)	0 (0)	0 (0)
Aztreonam	15.1 (10)	3.1 (2)	81.8 (54)	16.6 (2)	0 (0)	83.4 (10)
Ceftazidime	21.2 (14)	3.1 (2)	75.7 (50)	25 (3)	0 (0)	75 (9)
Cefotaxime	25.7 (17)	4.5 (3)	69.7 (46)	16.7 (2)	8.3 (1)	75 (9)
Ceftriaxone	22.7 (10)	0 (0)	77.3 (51)	16.7 (2)	8.3 (1)	75 (9)
Gentamicin	15.1 (10)	1.5 (1)	83.3 (55)	0 (0)	0 (0)	100 (12)
Tobramycin	18.2 (12)	6.1 (4)	75.7 (50)	8.3 (1)	8.3 (1)	83.4 (10)
Ciprofloxacin	15.1 (10)	0 (0)	84.8 (56)	8.3 (1)	0 (0)	91.7 (11)
Cotrimoxazole	40.9 (27)	4.5 (3)	54.5 (36)	33.3 (4)	0 (0)	66.7 (8)

R: Resistance, I: Intermediate, S: Susceptible

Table III. Ciprofloxacin susceptibility of ESBL-producing and non-ESBL producing *Escherichia coli* isolates

Isolates		**Frequency of ciprofloxacin susceptibility (no.)**	
		Resistant	**Sensitive**
Klebsiella pneumonia (12)	ESBL-producing isolates	0	2
	Non ESBL-producing isolates	1	9
Escherichia coli (66)	ESBL-producing isolates	6	10
	Non ESBL-producing isolates	4	46

ESBL: Extended-Spectrum Beta-Lactamase

findings showed that ciprofloxacin-resistant isolates can also be found in children. A study in Yasuj, İran, reported an increase in the rate of resistance to ciprofloxacin in children (19). In a study by Domiinguez et al. (21), 5% of *E. coli* strains isolated from children were resistant to ciprofloxacin. Other studies in recent years have also documented isolates of quinolone-resistant *Enterobacteriaceae* in children (22,23). Reports from İran and other parts of the world demonstrated a significant correlation between the mutations in the chromosomal *gyrA* and *parC* genes and resistance to fluoroquinolones (24,25). In the present study, mutations were observed in the *gyrA* and *parC* genes among all isolates resistant to ciprofloxacin, and sensitive isolates also lacked mutation in these genes. Further, the average MIC level of fluoroquinolones was higher in those isolates with mutations in comparison to those isolates without mutations (p=0.001), which highlights the important role of mutations in resistance.

Recently, in a report from Spain, a mutation in the *gyrA* gene was found in isolates from infants, which play a role in resistance to quinolones (26). In our research, similar to a study by Huang et al. (6), the results of the sequencing of QRDRs from gyrA showed the presence of Ser83 → Leu + Asp87 → Asn mutations among quinolone-resistant isolates from children, as the most frequent mutations. In this study, the mutations in the

Table IV. gyrA and parC mutations in *Escherichia coli* and *Klebsiella pneumonia* isolates

	Gene	Amino acid position	Nucleotide changes	Amino acids substitute	No. of isolates (%)
gyrA	*Escherichia coli*	Serine83/Asp87	TCG→TTG	Leucine	10 (15.1)
			GAC→AAC	Asparagine	
		Serine83	TCG→ TTG	-	1 (1.5)
		WT	-	-	55 (83.3)
	Klebsiella pneumonia	Serine83/Asp87	TCC→TTC	Phenylalanine	1 (8.3)
			GAC→AAC	Asparagine	
		WT	-	-	11 (91.7)
parC	*Escherichia coli*	Serine80/Glu84	AGC→ATT	Isoleucine	3 (4.5)
			GAC→GTA	Valin	
		Serine80	AGC→ATT	Isoleucine	7 (10.6)
		WT	-	-	56 (84.8)
	Klebsiella pneumonia	Glu84	GAA→AAA	Lysine	1 (8.3)
		WT	-	-	11 (91.7)

Asp: Aspartic acid, Glu: Glutamic acid

Table V. Mutations in Quinolone resistance-determining regions of the *gyrA* and *parC* genes of *Escherichia coli* and *Klebsiella pneumonia* in isolates and their corresponding Minimum Inhibitory Concentrations for Ciprofloxacin

	Mutations in the QRDR				No. of isolates	MIC (µg/mL) range				
	gyrA		parC							
	Ser83	Asp87	Ser80	Glu84		<1	1-2	4-8	16-32	64-128
E. coli	Leu	Asn	Ile	Val	3	-	-	-	-	3
	Leu	Asn	Ile	-	7	-	-	2	4	1
	Leu	-	-	-	1	-	1	-	-	-
	-	-	-	-	55	46	9	-	-	-
K. pneumoniae	Phe	Asn	-	Lys	1	-	-	-	-	1
	-	-	-	-	11	8	3	-	-	-

Ser: Serine, Ile: Isoleucine; Leu: Leucine, Asp: Aspartic acid, Glu: Glutamic acid, Phe: Phenylalanine, Asn: Asparagine, Val: Valin, Lys: Lysine, QRDR: Quinolone resistance-determining region, MIC: Minimum Inhibitory Concentrations

gyrA and *parC* genes were similar to mutations in these genes of strains isolated from the adult population in our previous study (27). Another study also reported that the Ser83 → Leu + Asp87 → Asn mutation was similar to that of quinolone-resistant isolates from children and adults (6). In fact, it has been reported that resistant isolates might be transmitted from adults to children (6). The topoisomerase IV is a secondary target in the Gram-negative bacteria for fluoroquinolones (7). In those isolates with mutations in the QRDR region of the *parC* gene, the level of resistance to ciprofloxacin was higher, which is consistent with other studies that reported that the mutation in the topoisomerase IV reduces the sensitivity to quinolones (28).

In our study, the isolates with multiple mutations in the *gyrA* and *parC* genes showed that the MIC value of ciprofloxacin was higher compared to isolates with single or no mutation. These results indicate that multiple mutations are required in these genes to induce high levels of resistance to fluoroquinolones. Faghri et al. (28) reported that it is necessary to have multiple mutations in the *gyrA* and *parC* genes for high levels of resistance to fluoroquinolones.

Conclusion

Resistance to ciprofloxacin is high in *E. coli* isolated from the pediatric population in Iran. Given that the use of ciprofloxacin in pediatric UTIs is limited, the presence of this fluoroquinolone resistance alone cannot be due to antibiotic selective pressure. At the same time, the mutations in the *gyrA* and *parC* genes in *E. coli* isolated from children were similar to those of adults, indicating the possibility of the transference of these resistant isolates from adults to children.

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Ethics

Ethics Committee Approval: The study was approved by the Kermanshah University Ethics Committee (approval number: 2016/241).

Informed Consent: All patients were hospitalized in an university hospital and a free and informed consent was obtained from each participatnts.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Design: K.G., A.A., A.E., S.J., R.C., Data Collecting or Processing: K.G., A.A., A.E., S.J., R.C., Analysis or Interpretation: K.G., A.A., A.E., S.J., R.C., Literature Search: K.G., A.A., A.E., S.J., R.C., Writing: K.G., A.A., A.E., S.J., R.C.

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Original Article

Extended-focused Ultrasonography for Children with High-energy Trauma

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ABSTRACT

Aim: Ultrasonography (USG) is an important tool used in the diagnosis of critical patients. The present study was carried out in order to detect intra-peritoneal free liquid in cases with high-energy trauma by using "extended-focused trauma (E-FAST) USG" and to determine the diagnostic power and benefits of this method.

Materials and Methods: The medical records of pediatric cases with high-energy trauma were examined retrospectively. The results of computed tomography (CT) and radiologist-operated abdominal (Rad) USG and the demographic data of patients were compared with the results obtained from E-FAST-USG performed by a pediatric emergency specialist. Chi-square test was used to compare the categorical measurements among the groups.

Results: One hundred and sixty patients were observed during the study period. When E-FAST-USG was compared to Rad-USG, the accuracy rate of E-FAST-USG was found to be 97.5%, sensitivity to be 90.9%, and specificity to be 98%. Forty-one of the patients were examined using CT. The sensitivity of Rad-USG was found to be 64.6% and specificity to be 93.3%, whereas the sensitivity of FAST-USG was found to be 81.8% and specificity to be 93.3%.

Conclusion: FAST-USG can be used in pediatric trauma cases at high sensitivity-specificity levels, and the radiation exposure of CT, which is a major consideration during childhood, can be reduced.

Keywords: Pediatric emergency, extended-focused trauma ultrasonography, high-energy trauma

Introduction

Children differ from adults in both anatomical and physiological aspects. As a result, general body trauma management includes significant differences even though the general practices are similar. Since the body mass index is low and surface/weight ratio is high among children, children may be exposed to trauma with higher levels of energy when compared to adults. For this reason, trauma may be more likely to cause multiple systemic injuries, morbidity, and mortality among children compared to adults (1,2).

By using extended-focused trauma ultrasonography (E-FAST-USG), the free fluids in the pericardial and pleural spaces and the pneumothorax can be easily detected in children with high-energy trauma (2). In accordance with the Advanced Trauma Life Support Protocol, it is recommended to apply E-FAST-USG immediately after an initial examination (3).

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USG began to be used in emergency units in the 1990s by emergency medicine specialists who had been trained for USG, and the first guideline was published in 2001. Subsequently, articles were published between 2009 and 2012 by the Council of Emergency Medicine Residency Directors. However, there is no specific guideline in use today (4). As in our department, the use of USG has become more popular in pediatric emergency units.

During trauma management, radiography and computed tomography (CT) are more commonly used. However, since exposure to radiation during childhood may lead to later malignancy, this subject should be given importance (5). In the present study, we aimed to determine the contribution of E-FAST-USG, which is fast and reliable and has no radiation component, on treatment management.

To our knowledge, the present study is the first study on identifying the presence of intra-peritoneal free fluids (IFF), pericardial tamponade, and pneumothorax using FAST-USG by a pediatric emergency physician trained for USG in pediatric trauma patients in Turkey and on the comparison of FAST-USG with Rad-USG and CT.

Materials and Methods

In the present study, after the approval of Çukurova University Faculty of Medicine Non-interventional Clinical Research Ethics Committee (approval number: 12/59, date: 2016), the emergency records of patients admitted to the Pediatric Emergency Department of the Medical Faculty of Çukurova University between February 2015 and July 2016 were retrospectively analyzed by a single researcher. Those cases with penetrating trauma were excluded from the study. After an initial examination, the pediatric emergency specialist physician applied E-FAST-USG to the cases within the first hour, prior to radiological examination. From the files of the patients, the type of injury, vital findings, complete blood counts, biochemical laboratory results, presence of hematuria, duration of hospitalization, and surgical intervention data were collected. The results of FAST-USG, which was performed by a certified emergency pediatrician, the results of RAD USG, which was performed by a blinded radiologist and the results of abdominal CT were examined retrospectively and compared. Those cases having altered mental status, acute abdomen, undetectable bowel sounds, severe abdominal pain with sensitivity, swelling, bruising in abdomen, a decrease in hemoglobin, and those who were hemodynamically stable but were observed to have constantly increasing intraperitoneal fluid level in E-FAST imaging were taken for abdominal CT in our department (1). In the first examination, the Sonosite Edge USG device and low-resolution convex probe (5-2 MHz), which can perform compound imaging, were used in the supine position in order to search for intraperitoneal free fluid in the hepatorenal and splenorenal regions in coronal cross-section and in perivesical areas in transverse and longitudinal cross-sections, and the cardiac examination was performed using sub-xiphoid imaging (Figure 1). Following this, by using 15-6 MHz linear probe, the presence of pneumothorax was sought in the junction of both the 2nd and 4th hemithoracic intercoastal space and anterior axillary line. The disappearance of pleural shifting motion and comet tail artifact lines (B lines), appearance of lung point, and barcode appearance in M-mod (time-motion mode) imaging were considered as pneumothorax, and the results were recorded.

Statistically Analysis

The data were analyzed using the IBM SPSS Statistics 20.0 program, and chi-square test was used in comparing the categorical measurements. The statistical significance was set to $p<0.05$. Assuming that all cases had undergone CT, the Begg&Greenes correction was performed, and the same statistical analyses were performed.

Results

A total of 160 cases were involved in the present study (102 boys and 58 girls). The mean age was 115±74 months (median: 123 months, interquartile range= 42.25-183.25 months).

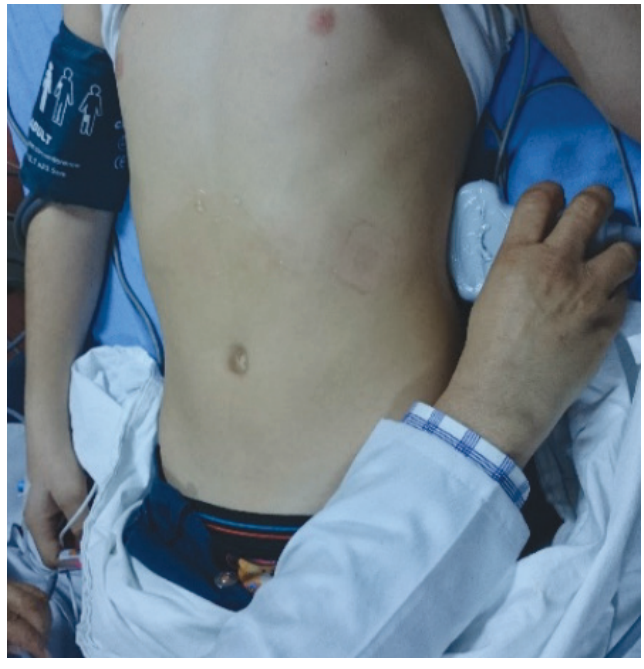

Figure 1a. A photo from an intervention in our department

The most common reason for admission was motor vehicle accident (52.5%), followed by falling from height (49 cases, 30.6%) (Table I).

IFF was detected in 13 (8.1%) patients by FAST-USG and in 11 (6.9%) patients by Rad-USG. (Figure 2) The comparison between FAST-USG and Rad-USG is presented in Table II.

In 2 of 3 cases, in which IFF was detected using FAST-USG but not with Rad-USG, CT imaging revealed the presence of IFF. In a case in which the IFF was detected by Rad-USG, but no IFF was found by FAST-USG, CT imaging revealed no IFF.

Abdominal CT was performed for 41 patients (25.6%) in the present study. IFF was positive in 11 (26.8%) of them. IFF was detected by FAST-USG in 9 of these 11 patients (81.8%) and by Rad-USG in 7 of these patients (63.6%) (Tables IIa and III).

FAST and Rad-USG methods were found to be statistically coherent to each other (Table IIb).

Table I. Reasons for patients' admissions to the emergency unit

Reason for admission to the emergency unit	Number of patients (n)	Percentage (%)
Motor vehicle accident	84	52.5
Falling from height	49	30.6
Other	27	16.9

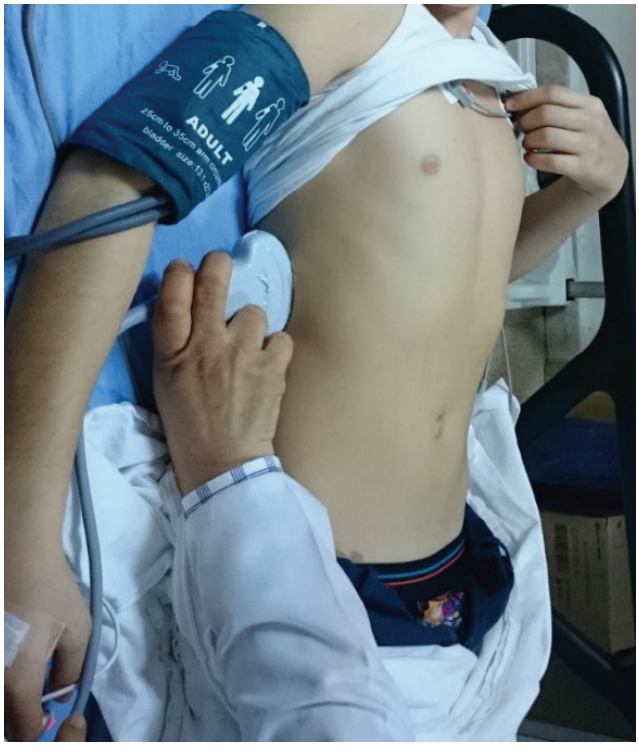

Figure 1b. A photo from an intervention in our department

In 30 cases in which no IFF was detected by CT, IFF was positive by FAST-USG for 2 cases. In one of these cases [in which IFF (+) was reported by FAST-USG, but IFF (-) by CT], minimal liver contusion was reported by CT. In the other case, pseudo-positive free fluid was observed using Rad-USG. The sensitivity of the FAST-USG method was 81.8%, and the specificity was 97.3% (Table IV).

One patient's Rad-USG was IFF (+) but abdominal CT and FAST-USG were (-). In 2 of 3 cases, Rad-USG was IFF (-), but FAST-USG and abdominal CT were (+).

It was assumed that all patients had undergone abdominal CT; thus, Begg&Greenes correction was applied, and the calculations were repeated. After recalculation, it was determined that the method is highly selective (98.2%) and more sensitive (52%) when compared to Rad-USG (Table V).

In the first examinations of 13 patients found to have IFF by FAST-USG, 3 had hypotension, 6 had tachycardia, and 4 had tachypnea-bradypnea. In physical examinations, abdominal sensitiveness was detected in 8 patients. The hematocrit levels of 4 patients were decreased during the observation, but none of them required blood-product support.

One of 13 patients who was found to have IFF by FAST-USG died due to severe head trauma during the intensive care observation without the need for intra-peritoneal surgery. Eight patients were managed conservatively and laparotomy was performed for 4 patients. Three of those four patients underwent splenectomy, nephrectomy or bladder reconstruction procedures. Due to laceration, a drain was placed in the liver of one patient. One patient died and 4 patients who needed surgical intervention were

Table IIa. Comparison between Focused trauma-ultrasonography and Radiologist-operated abdominal-ultrasonography

	Rad-USG (+)	Rad-USG (-)	Total
FAST-USG (+)	10	**3**	13
FAST-USG (-)	**1**	146	147
Total	11	149	160

FAST-USG: Focused trauma-ultrasonography, Rad-USG: Radiologist-operated abdominal-ultrasonography

Table IIb. Kappa fit index

Fit index (Kappa)	Accuracy rate	Sensitivity	Selectivity
0.82	97.5%	90.9%	98%

under observation in the intensive care unit. The other seven patients in the surgery department and the other 2 patients in the emergency department unit were observed.

Additionally, in two cases, in which pneumothorax was detected by the E-FAST-USG method with disappearance of pleural shifting motion, determining the lung point and achieving the barcode appearance in M-mod examination, the pneumothorax diagnosis was supported with radiographic results but it was determined that the patients required no intervention and they recovered spontaneously (Figures 3 a-b).

Discussion

The clinical statuses of patients having blunt abdominal trauma may not be obvious at the initial examination. For this reason, repeated examination, laboratory analyses, and imaging are needed. If blunt abdominal trauma is not diagnosed or not treated sufficiently, mortality may result (5).

FAST-USG was first named by Rozycki in the early 1990s, and it began to be used routinely by emergency physicians in the initial examinations of patients (5-8). Over time, it became an integral part of advanced life support (8,9). In previous studies, it was reported that the success rate of healthcare professionals in IFF imaging using the FAST method increased after having USG training (10).

As a non-invasive, affordable, and repeatable method with no radiation exposure, FAST-USG offers ease of use for the management of patients with general body trauma, but it may be disadvantageous since it depends on the experience of the operator (6,11). It yields rapid and accurate results, but it may be incapable of detecting the origin of IFF or showing solid organ damage (12,13). When compared to USG, CT depends less on the operator and it can show organ damage, but exposure to radiation is inevitable for the children (11).

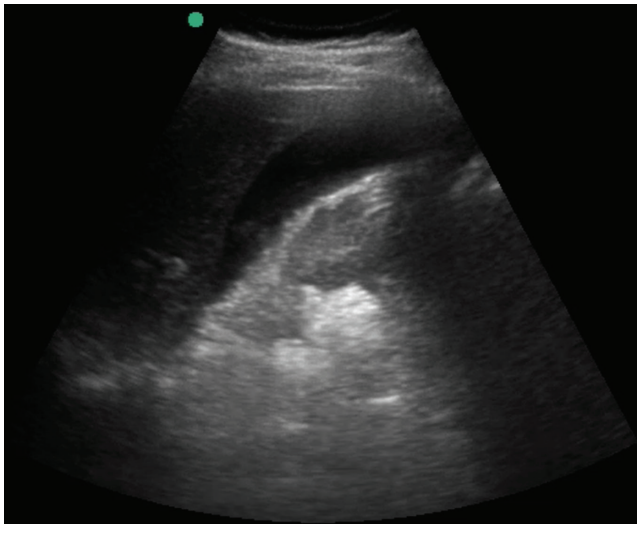

Figure 2. An image of free fluid in spleno-renal area

In the present study, the efficiency of FAST-USG for the examination of children having general body trauma was compared with CT and Rad-USG. When compared to Rad-USG, the sensitivity of FAST-USG was found to be 90.9% and its specificity to be 98% [Area Under the Curve (AUC): 97.5%]. In line with the literature, the results of the present study indicate that this method is viable and reliable to a good degree (8,14-17).

In Turkey, there have been a few studies carried out by emergency physicians on examining the reliability of the FAST-USG method. One of them was conducted by Uz et al. (9) on 107 adults, in which they determined

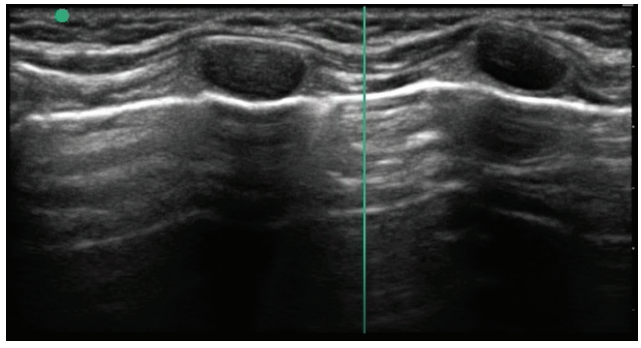

Figure 3a. A pneumothorax image from the study

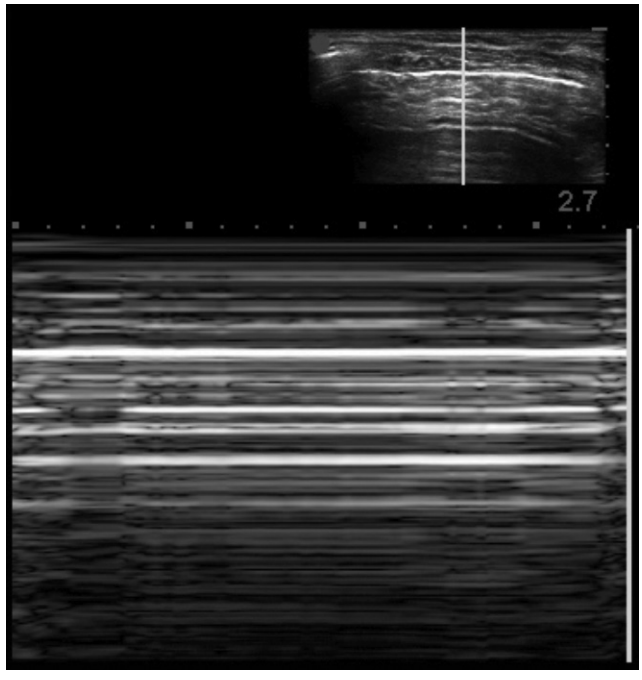

Figure 3b. A pneumothorax image from the study

Table III. Comparison between the data of computed tomography, focused trauma-ultrasonography, and radiologist-operated abdominal-ultrasonography

	BT-SS (+)	BT-SS (-)		BT-SS (+)	BT-SS (-)
Rad USG (+)	7	2	FAST-USG (+)	9	2
Rad USG (-)	4	28	FAST-USG (-)	2	28
41	11	30	-	11	30

FAST-USG: Focused trauma-ultrasonography, Rad-USG: Radiologist-operated abdominal-ultrasonography

Table IV. Reliability values of focused trauma and radiologist-operated abdominal-ultrasonography methods in comparison with computed tomography

	Sensitivity	Selectivity	Positive-Predictive Value	Negative-Predictive Value
Rad-USG	63.6%	97.3%	63.6%	97.3%
FAST-USG	81.8%	97.3%	69.2%	98.6%

Rad-USG: Radiologist-operated abdominal-ultrasonography, FAST-USG: Focused trauma-ultrasonography

Table V. Comparison of radiologist-operated abdominal-ultrasonography and focused trauma-ultrasonography with the computed tomography method after Begg&Greenes correction

	Sensitivity	Selectivity
Rad-USG	31.5%	98.2%
FAST-USG	52%	98.2%

Rad-USG: Radiologist-operated abdominal-ultrasonography, FAST-USG: Focused trauma-ultrasonography

intra-abdominal injury and hemothorax by the E-FAST-USG method compared to the gold standard method of CT. Also, Uz et al. (9) reported the sensitivity levels of the methods to be 54.5% and 71%, respectively, and no surgical intervention was necessary for those patients who had IFF but the E-FAST method did not revealed the presence of IFF. In the same study, Uz et al. (9) determined that the E-FAST-USG method identified pneumothorax with 81.8% sensitivity and 100% specificity. To the best of our knowledge, the present study is the first one that has been carried out by pediatric emergency physicians in Turkey.

Ianniella et al. (18) carried out a study on 368 patients with unstable hemodynamics by CT examination as a reference; they reported that the E-FAST method had 80% sensitivity and 99.8% specificity (AUC: 97.2). Among our patients, two patients were diagnosed with pneumothorax using both X-ray and E-FAST-USG methods, and no CT imaging was applied to these patients during the observation period. No surgical intervention was required during observation.

In the literature, the sensitivity and specificity of the FAST-USG and Rad-USG methods were reported to be 52%-100% and 96%-99% respectively (8,14-16). Zamani et al. (8) compared the Rad-USG and FAST-USG methods for 138 patients aged between 4 and 65 years and they reported the sensitivity and specificity of FAST-USG to be 84.6% and 97.6%, respectively.

Menaker et al. (19) emphasized that FAST-USG might reduce the use of abdominal CT in cases in which the physicians are suspicious of low- and mild-level intra-abdominal injury.

Of the 160 patients whose files we examined, 41 had undergone abdominal CT. Eleven patients had IFF. The presence of fluid was detected using FAST-USG in 9 of these patients. In CT examinations of the remaining two patients, free fluid was found in the hepatorenal area of one patient, and hematoma was detected in the presacral area of the other patient. Since there was no indication due to other clinical or laboratory findings, the other patients were not taken for CT imaging. Our patients were observed using repeated physical examination, laboratory analyses, FAST, and Rad-USG methods. The FAST-USG method, which is believed to be reliable to a good degree based on the results of the present study, may significantly contribute to the observation of pediatric patients with trauma in emergency departments and it may also limit radiation exposure by reducing the need for CT imaging.

Similar to the present study, Faruque et al. (17) also reported in their study, in which they confirmed the images of 31 cases by using CT imaging and they applied FAST-USG to 174 patients aged between 0 and 14 years, the sensitivity of the method was 91% and the specificity level was 95%. In a study by Schleder et al. (20), in which the authors

accepted CT as the gold standard, they detected IFF in 31 patients using FAST-USG and reported the sensitivity to be 75% and specificity to be 100%.

FAST-USG can be used as the initial examination and scanning test, and it may enable observation without CT examination for patients with stable hemodynamics (21). In the literature, there are few studies on the observation of pediatric patients with stable hemodynamics using only a repeated FAST-USG method (17,22). In the present study, in which the CT method was applied to 41 patients because of clinical suspicion or blunt abdominal trauma, 119 patients were observed using repeated USG in addition to clinical observation. In the literature, it is emphasized that unstable patients with blunt abdominal trauma should be taken to the operating room, and stable patients can be observed using repeated USG until there is a clinical change (17,23,24). Boutros et al. (25) studied 120 patients aged between 1 and 45 years and took the CT as reference and reported the sensitivity and specificity to be 93% and 99% for FAST-USG. In addition, they reported that three patients with unstable hemodynamics were directly taken to the operating room. On the other hand, it is also stated in literature that CT imaging might be necessary since USG might be insufficient in those patients in whom retroperitoneal injury is suspected (26).

Natarajan et al. (11), in their study carried out on 2.105 patients, 88 of whom had positive findings and taking diagnostic peritoneal lavage and CT as reference, showed that, different from the literature and the present study, FAST-USG is not sensitive, but selective to a good degree similar to the present study (sensitivity: 43%, specificity: 99%).

Study Limitations

The present study has certain limitations such as being carried out retrospectively and not all patients having undergone CT imaging.

Conclusion

USG is an easy-to-apply and non-invasive bedside method that can be used as a scanning test for pediatric patients with trauma. Since surgical intervention is not always necessary for those patients with IFF, repeated USG imaging may be required. Thus, the patient can be observed while limiting radiation exposure. At the same time, it may also enable a child with unstable hemodynamics to be taken immediately to the operating room after a positive FAST-USG.

Ethics

Ethics Committee Approval: Approved by Çukurova University Faculty of Medicine Non-interventional Clinical Research Ethics Committee (approval number: 12/59, date: 2016).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.T.K., H.L.Y., T.Ç., S.S.G., A.K.Ö., Concept: Ö.T.K., Design: Ö.T.K., Data Collection or Processing:Ö.T.K., H.L.Y., T.Ç., S.S.G., A.K.Ö., Analysis or Interpretation: Ö.T.K., İ.Ü., Literature Search: Ö.T.K., Writing: Ö.T.K., H.L.Y.

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Original Article

Necessity of Electroencephalography in High-risk Brief Resolved Unexplained Event

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ABSTRACT

Aim: A brief resolved unexplained event (BRUE) is characterized by sudden alterations in an infant's breathing, color, tone, or responsiveness. The aim of this study was to evaluate the necessity of electroencephalography (EEG) in high-risk BRUE cases.

Materials and Methods: Fifty-one patients' cases were analyzed retrospectively. All of these patients were younger than 1 month so considered to be a high-risk group. The gestational week, the age of the patient, the duration of the event, the conditions related to the event, whether or not any intervention was needed, the type of intervention if done, if the event recurred, the number of recurrences, the state of consciousness during the event, respiratory pattern, muscle tone, sleeping position, suspicion of trauma, use of medication by mother and/or baby and smoking exposure were evaluated in detail.

Results: The mean age of the patients was 15.74±14.96 days, 31 (60.78%) were male and 20 (39.21%) were female. The mean gestational age was 37.64±2.35 weeks. The neurological examinations of the patients were evaluated as normal. EEG was performed in 36 (70.58%) of the 51 patients and only one patient had sharp waves in the left hemisphere central region. In 11 patients hospitalized with a preliminary diagnosis of BRUE, final diagnoses were found as congenital pyloric stenosis, dehydration, fetal myocarditis, patent ductus arteriosus, lower respiratory tract infection and gastroesophageal reflux.

Conclusion: It would be more appropriate to plan the tests to be carried out in the high-risk BRUE group by evaluating many factors such as recurrence of the event, family history, and neurological examination findings. As a result, even in the high-risk BRUE group, it would be cost effective to perform an EEG if only the clinical cues are strongly suggestive for the diagnosis of epilepsy.

Keywords: Brief resolved unexplained event, high risk, electroencephalography

Introduction

The scope of brief resolved unexplained event (BRUE) and apparent life-threatening event (ALTE) definitions overlap but they are not completely identical. The main difference is that for an event to be labeled BRUE, it should be unexplained after an appropriate history and physical examination (1). In May 2016, the American Academy of Pediatrics (APA) recommended the use of the term BRUE instead of the previously used ALTE by the issue of a guideline (2). The BRUE term underlines that it is a non-life-threatening, temporary event with the lack of any clear reason. BRUE is defined as a sudden, short-term and resolved event in infants younger than one year of age. At

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least one of the following characteristics should be present in these attacks:

1. Cyanosis or pallor,

2. Absent, decreased or irregular breathing,

3. Marked change in muscle tone,

4. Altered level of responsiveness.

Sudden infant death syndrome (SIDS), seizures, central nervous system (CNS) abnormalities, cardiac problems and child abuse are some of the conditions that should be considered for the differential diagnosis of an infant brought in with a life threatening event and there is no consensus as to which diagnostic tests are required in these infants (1,3,4). Patients who were defined as BRUE in the APA guideline were divided into low and high-risk groups according to history and physical examination findings. Patients in the low risk BRUE group should have the following characteristics:

1. Age must be greater than two months,

2. Gestational age ≥32 weeks and post-conceptional age ≥45 weeks,

3. First BRUE,

4. Duration of event <1 minute,

5. No cardiopulmonary resuscitation required by trained medical personnel,

6. No concerning historical features or physical examination findings.

In the lower-risk group, clinicians are advised to inform the family, also they may briefly monitor oxygen saturation with pulse oximetry, and may obtain an electrocardiography. In addition, routine electroencephalography (EEG) is not advised in this lower-risk group (2). According to the APA guideline, high-risk BRUE is a diagnosis based on history and physical examination, and requires further investigation (2).

The aim of this study was to evaluate the necessity of EEG in high-risk BRUE cases.

Materials and Methods

Patient records of the Neonatal Intensive Care Unit at Ege University Medical Faculty were retrospectively analyzed. Those patients who were followed up with a diagnosis of BRUE between January 2017 and January 2018 were included in the study. All of the patients were younger than 1 month so considered to be in the high-risk group. The gestational week, the age of the patient, the duration of the event (<1 minute, 1-5 minutes, >5 minutes), the conditions related to the event, whether or not any intervention was needed, the type of intervention if done, if the event recurred, the number of recurrences, the state of consciousness during the event, respiratory pattern, muscle tone, sleeping position, suspicion of trauma, use of medication by the mother and/or baby and smoking exposure were evaluated in detail. The neurological evaluation of patients, EEG, cranial ultrasonography (USG), cranial magnetic resonance imaging (MRI) and final diagnosis were recorded. This study was approved by the Ege University Local Ethics Committee under the approval number: 18-9.1/35 and was conducted in accordance with the principles of the Declaration of Helsinki. All of the parents of the patients gave their informed consent prior to their child's inclusion in the study.

Statistical Analysis

Statistical analyses were conducted using SPSS 22.0 for Windows (SPSS Inc., Chicago, IL). Descriptive analysis was used and variables was given as frequency and percentage.

Results

A total of 51 patients who were followed-up with the diagnosis of BRUE were included in this study. The mean age of these patients was 15.74±14.96 days, 31 (60.78%) were male and 20 (39.21%) were female. The mean gestational age was 37.64±2.35 weeks. The duration of the event was <1 minute for 33 (64.70%) patients, 1- 5 minutes for 16 (31.37%) patients and >5 minutes for 2 (3.92%) patients. The event occurred in the postprandial period in 27 patients. It was associated with vomiting in 9 patients and crying in 2 patients. In two patients, the event occurred during sleep and 15 patients did not have any associated event. Ten patients were intervened with via tactile stimuli and no other intervention was performed. Eleven of the patients had a recurrence in the first 24 hours. A change in responsiveness was observed in four patients. Forty patients were in a supine position at the time of the incident. The lying position was not known in 11 patients. Fourteen patients had apnea, but no change of breathing pattern was reported in the remaining patients. According to the information obtained from the families, 14 patients had decreased muscle tone and 9 cases had increased muscle tone during the event. None of the patients had a history or suspicion of trauma. Four patients had a history of anti-reflux treatment (sodium alginate and magnesium alginate) and one patient had phenobarbital use. While there was no history of maternal drug use, two patients had a history of smoking in both parents. None of the patients had a family history of epilepsy. Neurological examination of the patients was performed by pediatric

neurologists and all were evaluated as normal. Cranial USG was performed in 44 patients and abnormalities were detected in 3 patients (germinal matrix hemorrhage grade 1, cavum septum pellucidum and slit ventricle). The patient with slit ventricles in cranial sonography underwent cranial MRI which was found to be normal. EEG was performed in 36 (70.58%) of the 51 patients and only one patient had sharp waves in the left hemisphere central region. This patient was on phenobarbital treatment which was started at another hospital due to the suspicion of seizure. Cranial MRI was normal. Phenobarbital treatment was discontinued because the patient was seizure-free. This patient did not have recurrences. Follow-up and EEG control were found to be normal.

In 11 patients hospitalized with a preliminary diagnosis of BRUE, final diagnoses were found as congenital pyloric stenosis (1 patient), dehydration (1 patient), fetal myocarditis (1 patient), patent ductus arteriosus (1 patient), lower respiratory tract infection (3 patients) and gastroesophageal reflux (4 patients).

Clinical features of patients are summarized in Table I.

Discussion

The existence of a life-threatening event in infancy often requires extensive investigations. However, even after extensive research, approximately 40% of these events remain unexplained. Therefore, a detailed history and physical examination are considered as the most accurate diagnostic methods before the implementation of expensive investigations (3).

The mean age of the patients was 15.74±14.96 days and the mean gestational week was 37.64±2.35 weeks. We evaluated all of our patients to be in the high-risk group because they were all younger than 2 months of age.

ALTE/BRUE may be the first sign of epileptic seizure in children. Neurological assessment, including neuroimaging and EEG, is often obtained because of concerns that seizures or other CNS pathologies may cause a life-threatening event. However, in the studies conducted, it was observed that the risk of long-term epilepsy ranged between 3% and 11% in patients with ALTE (4,5).

Bonkowsky et al. (4) retrospectively evaluated 471 patients hospitalized after a life-threatening event and found that only 3% of these patients were diagnosed with epilepsy. In 71% of the patients who developed epilepsy, the second incident occurred within one month of the first event. EEG was performed in 156 (33%) of the patients and only 6 (1.3%) patients had abnormalities. While two of these patients had post neonatal epilepsy, 11 patients with post neonatal epilepsy had normal EEGs at the time of the first event. The sensitivity of EEG in the prediction of post neonatal epilepsy was low (13%). In addition, it was emphasized that the neurological evaluation performed during ALTE had a low value in predicting post neonatal epilepsy. In our study, a recurrence of episodes occurred in eight patients within the first 24 hours, while none of the patients had recurrences in the following one month. EEG was abnormal in only one (2.7%) of 36 patients.

In another study, 172 patients with recurrent ALTE were evaluated. Seventeen patients with normal interictal EEG's had clinical features suggesting focal epilepsy. All patients underwent continuous monitoring for EEG and other physiological parameters (breathing, electrocardiogram, oxygen saturation). Six patients had EEG abnormalities preceding physiological changes consistent with ALTE (6).

Nunes et al. (7) presented six children displaying a first episode similar to ALTE who were ultimately diagnosed with epilepsy. The neurological examinations and neuroimaging findings of these patients were found to be abnormal. These patients also had family history of epilepsy and SID.

Tirosh and Jaffe (8) evaluated 46 patients with ALTE and found that seven patients had CNS disorders such as convulsion, developmental retardation, intraventricular hemorrhage, hydrocephalus and corpus callosum agenesis. However, these patients had recurrent episodes of ALTE, episodes requiring resuscitation, abnormal neurological examination findings and a family history of epilepsy. In addition, the first EEG was normal in some patients and EEG abnormality was only detected in follow-up EEGs. The patients included in our study did not have a family history of epilepsy and their neurological examinations and neuroimaging were found to be normal. Eight patients had recurrent episodes but none of the patients required resuscitation.

In another study evaluating the contribution of EEG to ALTE, EEG was performed in 15 of 47 patients with ALTE and abnormalities were found in two cases. As a result, the authors reported that EEG had low additional value (13%) in ALTE (9). Genizi et al. (3) found that, of the 15 patients diagnosed with clinical seizures, only one had abnormal interictal EEG. In our study, EEG was abnormal in only one case.

We did not find any signs suggesting trauma or child abuse in any of our patients. All had normal neurological examinations, and no family history of epilepsy or SID. One patient had an abnormal EEG and phenobarbital treatment

Table I. Clinical features of the patients

Patient no	Sex/age (days)	Gestational week	Recurrence	EEG	TFUSG	Final diagnosis
1	M/23	41		Normal	Normal	
2	M/6	40	1	Normal	Abnormal	
3	M/12	37		ND	Normal	Lower respiratory tract infection
4	M/5	38		Normal	Normal	
5	M/24	35		ND	Normal	
6	M/21	39		Normal	Normal	Congenital pyloric stenosis
7	M/15	39		ND	Normal	
8	M/31	32		Normal	Normal	
9	M/3	38		ND	ND	Dehydration
10	F/1	36		ND	Normal	Gastroesophageal reflux disease
11	F/2	39		ND	ND	
12	M/1	38		Normal	Normal	
13	M/2	34		Normal	Normal	
14	F/1	37		Normal	Normal	
15	M/2	39	1	ND	Normal	
16	M/8	40		ND	ND	
17	M/59	33		Normal	Normal	Patent ductus arteriosus
18	F/1	41	1	ND	Normal	
19	F/17	40		Normal	Normal	
20	M/24	39		ND	ND	Gastroesophageal reflux disease
21	F/8	37	1	ND	ND	
22	F/2	40		Normal	Normal	
23	M/25	38	2	Abnormal	Normal	
24	M/10	38		Normal	Normal	
25	K/53	33	3	Normal	Normal	Gastroesophageal reflux disease
26	K/53	33	3	Normal	Normal	Gastroesophageal reflux disease
27	M/12	37	2	Normal	Normal	
28	F/18	37		Normal	Normal	Lower respiratory tract infection
29	F/52	30	2	Normal	Normal	
30	M/20	36	2	Normal	Normal	Lower respiratory tract infection
31	M/3	40		Normal	Normal	
32	F/15	38	2	Normal	Normal	
33	M/28	38		Normal	Normal	
34	F/2	40		ND	Normal	
35	M/11	39		Normal	Normal	
36	M/37	36		ND	ND	
37	F/37	35		Normal	Abnormal	
38	F/27	39		Normal	Normal	
39	M/13	38		Normal	Normal	

Table I. Continued

Patient no	Sex/age (days)	Gestational week	Recurrence	EEG	TFUSG	Final diagnosis
40	F/10	39		ND	Normal	
41	M/6	38		Normal	Normal	
42	M/14	39		ND	ND	
43	M/8	37		Normal	Normal	
44	M/2	39		Normal	Normal	
45	F/12	38		Normal	Normal	
46	M/25	37		ND	Normal	
47	F/7	40		Normal	Normal	
48	M/3	38		Normal	Normal	
49	F/2	40		Normal	Normal	
50	F/11	38		Normal	Normal	Fetal myocarditis
51	M/19	38		Normal	Abnormal	

*ND: Not done, EEG: Electroencephalography, TFUSG: Transfontanelle ultrasonography

was started at another hospital due to the suspicion of seizure. She had no recurrence during follow-up and phenobarbital was tapered within one month. Her control EEG obtained 3 months later was normal.

McGovern and Smith (5) reviewed eight studies, including 643 infants (0-13 months) in terms of the etiology of ALTE. The most common final diagnoses were gastroesophageal reflux (31%), seizure (11%) and lower respiratory tract infection (8%). 23% of the patients were not diagnosed (reason unknown). In this review, 5 deaths were reported in total and all of them occurred in infants with an underlying medical problem. In 11 (21.5%) of our patients, a detectable cause was found and the most common final diagnosis was gastroesophageal reflux (4 patients). This was followed by lower respiratory tract infection (3 patients), congenital pyloric stenosis (1 patient), dehydration (1 patient), fetal myocarditis (1 patient) and patent ductus arteriosus (1 patient).

Since most patients who develop post neonatal epilepsy will have a second episode within one month, delaying the initiation of antiepileptic drug will avoid potential morbidities associated with unnecessary exposure to these drugs (4). In addition, studies have shown that even if a patient is finally diagnosed with seizures/epilepsy, there is no difference in seizure remission between initiating treatment after the first seizure or the second seizure (10,11).

The American neurology academy recommends EEG after the first afebrile seizure, but its sensitivity after the first BRUE attack is quite low. Normal EEG cannot exclude seizures and an abnormal EEG is quite inadequate to predict epilepsy development (2).

Study Limitations

The retrospective nature of this study is the limitation of the study.

Conclusion

The risk of developing epilepsy after BRUE is unlikely to be determined by EEG alone. It would be more appropriate to plan the tests to be carried out by evaluating many factors such as recurrence of the event in the high-risk BRUE group, family history, and neurological examination findings. As a result, even in the high-risk BRUE group, it would be cost feasible to acquire an EEG if only the clinical cues are strongly suggestive for the diagnosis of epilepsy.

Ethics

Ethics Committee Approval: This study was approved by the Ege University Faculty of Medicine Clinical Research Ethics Committee (approval number: 18-9.1/35).

Informed Consent: All of the parents of the patients gave their informed consent prior to their child's inclusion in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.M.S., S.K., E.Ş., Concept: H.M.S., S.Y., G.A., D.T., Design: H.M.S., Ö.A.K., H.T.,

Data Collection or Processing: H.M.S., İ.D.Ç., E.Ş., D.T., S.K., Analysis or Interpretation: H.M.S., N.K., S.G., Literature Search: H.M.S., E.Ş., S.K., S.Y., Writing: H.M.S., S.G., E.Ş.

Conflict of Interest: The authors have stated that they had no interests which might be perceived as posing a conflict.

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Original Article

The Effects of Maternal Anemia in Pregnant Women with Respect to the Newborn Weight and the Placental Weight in the Delivery Room

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ABSTRACT

Aim: The aim of the study was to investigate the possible effects of maternal anemia in pregnant women with respect to placental weight and newborn weight.

Materials and Methods: In this cross-sectional study, 68 healthy pregnant women were included from the 2nd İzmir Atatürk Training and Research Hospital, Clinic of Obstetrics and Gynecology. Maternal anemia was defined with a hemoglobin value less than 10 g/dL. The correlations were studied between the parameters (hemoglobin levels, placental weight and newborn weight) in primiparous and multiparous women.

Results: The study cohort consisted of 36 (52%) multiparous and 32 (48%) primiparous women (mean age ± standard deviation: 27.40±7.23 years (range: 17-45 years). The mean age of the newborns was 39.8 weeks. The rate of gestational anemia was as 27%. The rate for multıparous pregnant women (31.7%) was four times higher rates anemia compared to the rate of primiparous pregnant woman (8.3%). A positive correlation was found between placental weight and child weight (R: 0.657, t value: 0.00). There was a weak negative correlation between placental weight and hemoglobin (Hb) values. However, there was no statistically significant correlation between maternal Hb values and neonatal weight.

Conclusion: Maternal anemia is an important and frequently encountered antenatal problem for pregnant women and it should be investigated in pregnant women and as well as candidates for pregnancy.

Keywords: Maternal anemia, placental weight, newborn weight

Introduction

Maternal anemia has been reported as the most common hematologic problem in pregnant women. This disorder occurs frequently as a result of insuffucient intake of iron and folic acid during pregnancy (1-4). It is reported that iron deficiency anemia occurs in 85-100% pregnant women with insufficient supplementation of iron during pregnancy (5,6). The rate and severity of maternal anemia has some variabilities in the different geographic and economical distribution (5). While many women in developed countries start pregnancy with low iron stores, this is much more serious in developing countries. Maternal anemia in the gestational period may also be related to obstetric complications such as postpartum hemorrhage, operative delivery and placental abnormalities (5,6).

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Maternal anemia might cause serious fetal and maternal complications during pregnancy (7). The effects of this disorder on the placenta and child weight have been reported in the several studies (8-11). Anemia with hemoglobin levels between 6-10 g/dL might cause placental hypertrophy during the pregnancy. A retrospective study from Oxford, England showed a correlation between maternal iron deficiency anemia and increased placental weight and placental/birth weight ratio (12). Some correlation between maternal anemia and low economic environment conditions and high morbidity of the newborn has been reported (13-17). Maternal anemia may also be associated with prematurity, low birth weight, miscarriages and even fetal death, even at moderate hemoglobin (Hb) levels of 8-11 g/dL (18,19).

The aim of this cross-sectional clinical study was to investigate the possible effects of maternal anemia in primiparous and multiparous pregnant woman with respect to placental weight and child weight in the west part of Turkey.

Materials and Methods

The study retrospectively included 68 pregnant women who were admitted to the 2nd İzmir Atatürk Training and Research Hospital, Clinic of Obstetrics and Gynecology.

Exclusion criteria was hereditary blood disease, systemic disease, hemorrhagic diathesis, non-gastrointestinal system disease that could lead to continuous blood loss, third trimester hemorrhage, premature rupture of membranes, hemolytic anemia and laboratory tests without Rh incompatibility.

A venous blood sample was taken from the pregnant women in the first stage of labor and Hb levels were measured. Gestational anemia was defined as a hemoglobin value of less than 10 g/dL. Weights of babies and placentas were measured in the delivery room by the same researcher (NT) after delivery.

Due to the commencement of labor, pregnant women were admitted to the clinic and the following parameters were recorded in order to compile the information in the patient files of all pregnant women: 1) Vital signs (body temperature, pulse, blood pressure, body weights and heights), 2) age, education level, socio-economic status, smoking and use of substances poor for the health, 3) complaints and anamnesis of application (systemic diseases such as diabetes, hypertension, heart failure, kidney disease, familial hematological diseases, presence of bleeding diathesis and previous operations), 4) obstetric anamnesis (gravid, parity, evacuation curettage, spontaneous abortion and number of living children), 5) presence of conditions that may make pregnancy risky in previous pregnancies, infant mortality, 3rd trimester and/or postpartum hemorrhage, how previous pregnancies ended, drug use, use of vitamins and especially iron preparations, diseases during pregnancy, trauma, surgery, 6) blood groups, 7) general systemic and obstetric examination (gestational week, fetal size, presentation, whether the presenting part is engaged, uterine tone during contraction and resting phase, etc.), 8) vaginal examination (cervical opening, wiping, coming part, height of the coming part, bone and soft tissue parts of birth canal) in patients with no bleeding that may be dangerous by examining whether there is bleeding in antenatal period in the current pregnancy.

The study was approved by Ethical Committee of Atatürk Training and Research Hospital (approval number: 47, date: 03.08.1999).

Statistical Analysis

In the statistical analysis, correlation between all biochemical and demographic parameters with Spearman Correlation Analysis test was investigated.

Results

Demographic Characteristics: The study included 36 (52%) multiparous and 32 (48%) primiparous women. The mean age of the pregnant women in the study cohort was 27.40 years [standard deviation (SD)+7.23 age range: 17-year-old primigravid and 45-year-old multigravida]. The mean gestational week of the newborns was 39.8 weeks of age (SD: 0.97).

Maternal Anemia, Placenta Weight and Child Weight: The maternal anemia was defined in 18 of 68 pregnant woman (27%). Multiparous pregnant women (31.7%) had four times higher rates of anemia compared to the rate of primiparous pregnant women (8.3%).

We compared the Hb levels and placenta weight of the pregnant woman and child weight at the delivery according the gravida number of the pregnant woman in the two groups (group 1: Primiparous versus, group 2: Multiparous). There were no statistically significant differences between two groups for the Hb levels, placenta weight and child weight respectively ($p=0.31$, $p=0.75$, $p=0.65$, $p>0.05$) in Table I.

The Correlation Between Maternal Anemia, Placenta Weight and Child Weight: A possible correlation was studied between the studied parameters (Hb, placental weight and child weight). There was no positive or negative

correlation between maternal Hb values and child weight (R: 0.26, t value: 0.41). However, there was a weak negative correlation between placental weight and Hb values in the whole group. (R: -0.23, t value: 0.02, R square: 0.56) (Figure 1). A positive correlation was found between placental weight and child weight. (R: 0.657, t value: 0.00) (Figure 2). However, there was no statiscally significant correlation (positive or negative) between maternal Hb values and child weight. (R: 0.26, t value: 0.41, R square: 0.00) (Figure 3).

Discussion

According to World Health Organization reports, maternal anemia has been reported as the most common form of anemia in pregnancy, which occurs as a result of insuffucient intake of iron and folic acid during pregnancy (20). In this study, the rate of maternal anemia was defined as 27% in the total cohort of primiparous and multiparous pregnant women. Multiparous pregnant women (31.7%) had four times higher rates of anemia compared the rate for primiparous pregnant women (8.3%).

The rate of anemia in pregnant women was compatible with the rates of reported in the previous studies (between 25% to 58%) (17-19). In their study, Prual et al. (21) reported the rate of gestational anemia at 25% of pregnant women in Chad. Lijestrand et al. (22) reported anemia in 58% of the pregnant women with Hb levels below 11.0 gr/dL in 58% of pregnant women. Our study and previous studies identified higher rates of gestational anemia in multiparous pregnant women compared with the rate of gestational anemia in primiparous women. These results indicate that the multiparous pregnant woman should be more carefully followed and supported with iron and folic acid supplementation.

In the present study we also studied the correlation between the parameters (Hb, placental weight and child weight). A positive correlation was found between placental weight and child weight. However, there was a weak negative

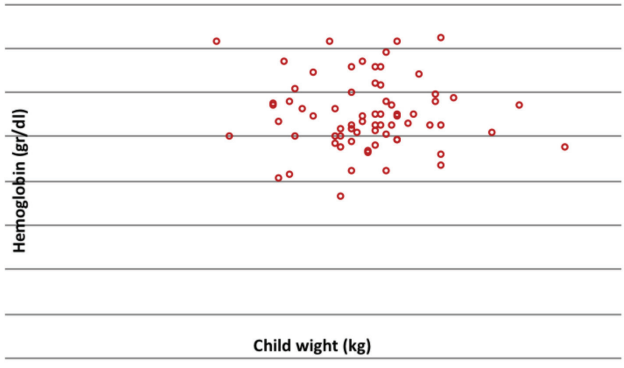

Figure 1. A weak negative correlation between placental weight and hemoglobin values (R: -0.23, t value: 0.02)

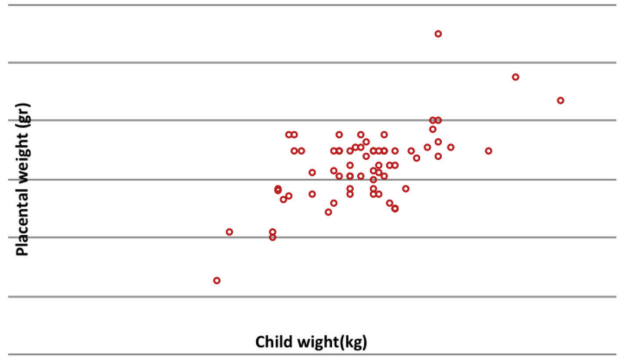

Figure 2. A positive correlation was found between placental weight and child weight (R: 0.657, t value: 0.00)

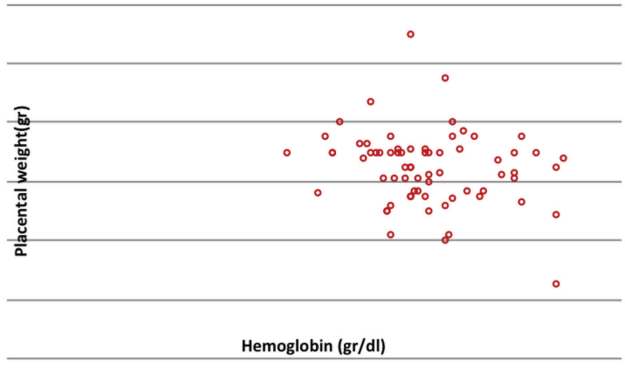

Figure 3. No statiscally significant correlation (positive or negative) between maternal hemoglobin values and child weight. (R: 0.26, t value: 0.41)

Table I. The comparison of hemoglobin, placental weight, and child weight in primiparous and multiparous pregnant woman

	Group 1	Group II	Total	p-value
	Primiparous Pregnant Woman	Multiparous Pregnant Woman	Pregnant Woman	
	n=32, Mean ± SD	n=36, Mean ± SD	n=68, Mean ± SD	
Hb (gr/dL)	11.27±1.37	10.88±1.69	10.99±1.60	0.31
Placenta weight (gr)	632.91±121.94	652.50±129.27	647.6±125.95	0.65
Child weight (kg)	3.13±0.49	3.30±0.54	3.25±0.55	0.75

SD: Standard deviation, Hb: Hemoglobin

correlation between placental weight and Hb values in the whole group. Wheeler et al. (23) reported that placental growth was determined by maternal factors prevailing before conception. They stated that maternal anemia is one of the environmental factors associated with increased placental weight at birth and thought that these factors modified angiogenesis in trophoblastic villi.

Previously, a few clinics studies reported that increased placental weight and hypertrophy are associated with maternal anemia. (4,24,25). The placenta weight to newborn weight ratio was found to increase in patients with anemia (26).

However, there was no statistically significant correlation (positive or negative) between maternal Hb values and child weight. However, although there is a contradiction in this issue in the literature, it has been found in some studies that placental weight increases with maternal anemia. In a prospective cohort study conducted by Williams et al. (27) in 1997 among 2507 pregnant women in Australia, placental weight was found to increase with maternal anemia. In the same study, gestational age was also positively correlated with an increase in placental weight. However, it was added that the ratio of placental weight to birth weight is not an accurate indicator for fetal growth. In a study conducted in 1991, it was reported that the higher the placental weight, the lower the Hb level and the mean maternal erythrocyte volume. The ratio of placental weight to birth weight was highest in the most anemic mothers. In addition, mother's smoking reduces placenta weight (28).

Study Limitations

There are several limitation of this cross-sectional study. First, the small number of patients in the present study is a major limitation of the study. This scarity did not allow us to conduct a etiologic subgroup categorization of maternal anemia (iron deficiency, folic acid deficiency Vitamin B12 deficiency, obstetric complications such as postpartum hemorrhage, operative delivery and placental abnormalities) as well as the the severity of gestational anemia. A second limitation is the lack of the histopathologic evaluation of maternal placenta. Thirdly, we did not conduct a follow-up measurement of the newborns at the 21st day of life to access the newborn weight without the maternal edema effects.

Conclusion

The placenta and fetal organ systems are able to compensate for maternal anemia without any major complications, that is, the child is somehow protected from anemia.

Ethics

Ethics Committee Approval: The study was approved by Ethical Committee of Atatürk Training and Research Hospital (approval number: 47, date: 03.08.1999).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

Conflict of Interest: None of the authors had conflict of interest.

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Original Article

A Cause of Fever that should be Kept in Mind in Family Medicine in Settlements Where Livestock Farming is Widespread: *Brucellosis*

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ABSTRACT

Aim: In our country, where animal husbandry is widespread, we aimed to examine retrospectively data concerning childhood *Brucellosis* cases, which are not very high in the literature, which may occur with many variable clinical findings and may cause misdiagnosis and serious complications.

Materials and Methods: The data of these patients with the diagnosis of *Brucellosis* who were treated between October 2016 and October 2018 in a Pediatric Clinic were retrospectively analyzed. For the diagnosis of *Brucellosis* in patients, the Wright agglutination test with complaints and clinical findings set at the titer being 1/160 or above was used.

Results: In our study, the mean age of the patients was 7.4 years (3-15). 52.12% (n=37) were male and 47.88% (n=34) were female. All patients had a risk factor for *Brucellosis* infection. In 88.7% (n=63) of these patients, consumption of milk and dairy products (precipitates, fresh cheese was not cooked), and 11.3% (n=8) of raw meat (raw meatball) consumption and animal contact history were determined.

Conclusion: Although early diagnosis and response to treatment with *Brucellosis* are very good, late diagnosis and inadequate treatment may cause mortality and morbidity with serious complications. Complaints of fatigue, weight loss and especially joint pain with long term fever should be evaluated by family physicians and pediatricians. The diagnosis of these patients should be kept in mind in the diagnosis of *Brucellosis*, an endemic disease common in our country.

Keywords: *Brucellosis*, child, fever

Introduction

Brucellosis is one of the zoonotic infectious diseases especially in developing countries, and it is still a significant public health problem worldwide (1). According to the data of the Ministry of Health in 2006, 10.810 cases with *Brucellosis* were detected in Turkey (2). *Brucellosis* is primarily a disease of animals, but it is also seen in humans living in settlements where animal husbandry is common. Transmission of *Brucella* species to humans; during the care and butchering of infected animals occurs by contact with the skin or by the consumption of the uncooked or undercooked meat or milk of these animals (1,3). Differential diagnosis is very important due to complaints and clinical findings of *Brucellosis* not being specific. The disease may present with variable clinical presentations especially in children, and usually begins

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with nonspecific symptoms after a 1-8 week incubation period (1,4). This situation may lead to late diagnoses and various complications (4,5).

Despite the variety clinical findings of *Brucellosis*, the most common clinical symptoms are fever (72.2-93.3%,), arthralgia/arthritis (46.6-73.7%), hepatosplenomegaly (6.7-20.6%). Other symptoms include abdominal pain, vomiting, headache, diarrhea, skin rash, night sweats, weakness, fatigue, weight loss, cough, pharyngitis and myalgia (6). The definitive diagnosis of the disease is made by producing the bacteria in culture (blood, bone marrow, cerebrospinal fluid). However, generally in the diagnosis of the disease, a serum agglutination test is used in clinical practice, the diagnosis is made if serum titer of the *Brucella* is 1/160 or above in this test (4,7-9). However, a delay in diagnosis and treatment, misdiagnosis and serious complications (neurobrucellosis, genitourinary complications, hematological findings, spondylitis, infectious endocarditis and encephalitis even death) may seen in the childhood period because of nonspecific symptoms of the disease.

The *Brucellosis* series in childhood period have not been reported commonly in the literature. The aim of this study is to retrospectively assess the data of our *Brucellossis* cases in childhood.

Materials and Methods

The data of 71 patients who were given a diagnosis of *Brucellosis* and were treated between October 2016 and October 2018 at the Faculty of Medicine, Department of Pediatrics, were retrospectively reviewed.

The diagnosis of *Brucellosis* was based on the complaints of the patients, clinical findings and Wright agglutination titer of 1/160 or above.

The medical data from the hospital medical records of risk factors of *Brucella* transmission (uncooked meat, milk and milk products consumption), demographic data, seasonal distribution, complaints of patients, time to diagnosis from onset of complaints, clinical and laboratory findings, family history were obtained.

Complete blood counts, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values, liver function tests, renal function tests and Wright agglutination test results were evaluated.

It was accepted that a hemoglobin levels below 10 gr/dL is anemia, a leukocyte level below 3.500/mm^3 is leukopenia, above 10.000/mm^3 is leukocytosis, a platelet value below 150.000/mm^3 is thrombocytopenia, below 20.000/mm^3 is severe thrombocytopenia (1).

Patients with chronic disease or immunodeficiency were excluded from the study.

This study was approved by Ethics Board of Mustafa Kemal University (approval number: 08/2018). All of the parents of the patients gave their informed consent prior to their child's inclusion in the study.

Statistical Analysis

The data was entered into the SPSS 20.00 program (SPSS Inc., Chicago, IL, USA,). Data was presented as percentage with minimum and maximum. Fisher's exact test or chi square test was used to compare between categorical variables groups. Mann-Whitney U test was used to compare continuous variables between groups. P level of <0.05 was accepted statistically significant.

Results

The mean age of the patients in our study was 7.4 years (between 3-15). 52.12% (n=37) were male and 47.88% (n=34) were female. All patients had risk factors for B*rucellosis* infection. These risk factors were the consumption of uncooked milk products (88.7% of patients (n=63) and consumption of uncooked meat and the anamnesis of contact with infected animals (11.3% of patients (n=8).

The seasonal distribution of the disease was 14.08% (n=10) in the autumn, 12.67% (n=9) in the winter, 33.80% (n=24) in the spring, 40.84% (n=29) in the summer months (Table I). The complaints of patients were as follows; fever 85.91% (n=61), weakness 94.36% (n=67), sweating 71.83% (n=51), anorexia 67.60% (n=48), knee-hip-low back pain 90.14% (n=64), abdominal pain 63.38% (n=45), weight loss 25.35% (n=18) and limb bruises 11.26% (n=8), scrotal pain 1.4% (n=1) (Table I).

The mean time from the onset of symptoms to diagnosis was 6 weeks (4-16). 78.87% (n=56) of the patients were acute and 21.12% (n=15) were subacute *Brucellosis*. Clinical findings were 91.54% (n=65), fever 87.32% (n=62), arthritis/arthralgia 90.14% (n=64), hepatomegaly 19.71% (n=14), splenomegaly 9.85% (n=7), petechia-purpura was 2.8% (n=2), scrotal swelling and redness 1.4% (n=1). Scrotal edema and hydrocele were detected in the ultrasonography of those patient with scrotal pain.

In the complete blood count of patients, 54.92% (n=39) had normal leukocyte (4000-10.000/mm^3), 18.30% (n=13) had leukocytosis (>10.000/mm^3), 26.76% (n=19) had leukopenia (<3500/mm^3), 36.61% (n=26) had anemia, 12.71% (n=9) had thrombocytopenia (<150000/

Table I. Features of patients		
	n	**%**
Demographic data		
Average age	-	7.4
Season		
Fall	10	14.8
Winter	9	12.67
Spring	24	33.8
Summer	29	40.84
Gender		
Male	37	52.12
Female	34	47.88
Incubation period		
Acute	56	78.87
Subacute	15	21.12
***Brucellosis* risk factor**		
Non pasteurized milk product consumption	63	88.7
Consumption of raw products dumplings	8	11.3
Complaints		
Fatigue	67	94.36
Joint pain	64	90.14
Fever	61	85.91
Sweating	51	71.83
Loss of appetite	48	67.6
Abdominal pain	45	63.38
Weight loss	18	25.35
Skin finding	8	11.26
Scrotal pain	1	1.4
Physical examination		
Fever	65	91.54
Fatigue	62	87.32
Arthritis/arthralgia	64	90.14
Hepatomegaly	14	19.71
Splenomegaly	7	9.85
Petechia/purpura	2	2.8
Scrotal swelling/redness	1	1.4
Laboratory values		
Normal leukocyte	39	54.92
Leukocytosis	13	18.30
Leukopenia	19	26.76
Anemia	26	36.61
Thrombocytopenia	9	12.71
Severe thrombocytopenia	2	2.81
Increased ESR	57	80.28
CRP elevation	59	83.09
Hematological parameters*		
Hemoglobin	7.6 (5.2-16.1)	
Leukocyte	$4.3x10^3$ ($2.7x10^3$-$17.4x10^3$)	
Platelets	$152 x 10^3$ ($17x10^3$- $165x10^3$)	

*Mean value (minimum-maximum)

mm³), 2.81% (n=2) had severe tombocytopenia (<20000/mm³).

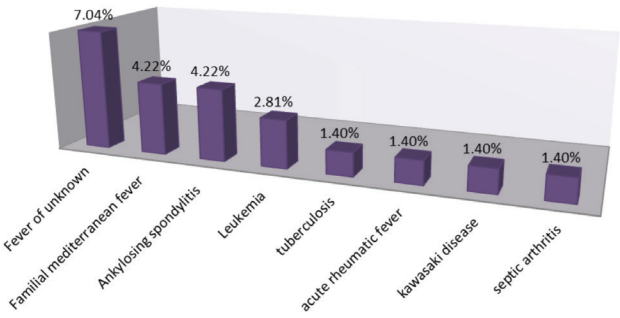
It was found that 80.28% (n=57) had increased ESR and 83.09% (n=59) had CRP elevation, and 36.61% (n=26) had increased transaminase levels. None of the patients had any signs of skin complaints other than thrombocytopenic petechia-purpura. During the first evaluation of the patients, using the Wright agglutination test, 85.91% (n=61) were found to be positive.

During the initial assessment for Wright agglutination test, 10 patients were negative despite having the diagnosis of *Brucellosis* with complaints, family history, *Brucella* transmission risk factors and clinical findings. However, when repeated after one week, the Wright agglutination test on these patients were positive. *Brucellosis* family history was found in 52.11% (n=37) of the patients. There were no mortal complications in any of the patients.

It was determined that in anamnesis, *Brucellosis* was confused with variable diseases; unknown fever 7.04% (n=5), leukemia 2.81% (n=2), tuberculosis 1.40% (n=1), ankylosing spondylitis 4.22% (n=3), acute rheumatic fever 1.40% (n=1), familial Mediterranean fever 4.22% (n=3), kawasaki disease 1.40% (n=1) and septic arthritis 1.40% (n=1) (Table II).

In treatment; for children under eight years of age; 8 mg/kg trimethoprim/sulfamethoxazole twice daily for six weeks and 30 mg/kg intramuscular (IM) streptomycin was administered at a single dose per day for three weeks. For

Table II. Uncertain/confusing clinical presentations



children over eight years of age; 100 mg oral doxycycline per 12 hours for 6 weeks and 5 mg/kg IM or intravenous gentamicin was administered daily for the first 7-10 days (10). Clinical improvement was observed in all patients.

Discussion

The studies concerning *Brucellosis* in the eastern regions of Turkey have reported that the consumption of uncooked milk and meat of infected animals were between 63% and 85% in the anamnesis of patients with *Brucellosis* (10,11). In our study, the risk factors for *Brucellosis* was similar to the literature (Table I). The incidence of *Brucellosis* was found to be low in winter and autumn and high in summer and spring months in studies (5,12,13). In our study, the seasonal distribution of the disease was found to be similar to the literature (Table I).

It is reported that there is no significant difference between gender in the incidence of *Brucellosis* in the literature. Although the disease can be seen in all age groups, it is more frequently seen in adolescents and young adults (3,5,11). As the clinical signs and symptoms of *Brucellosis* are not specific, it may cause diagnostic confusion. In our country, it has been reported that the most common complaints related to *Brucellosis* were fever, fatigue, loss of appetite, sweating, weight loss, joint pain (knee, hip, waist), abdominal pain and headache (3,5,14). Our study was similar to the literature (Table I).

In the evaluation of the patients with *Brucellosis* according to the duration of the symptoms, it was determined as follows; for acute cases it was between 0 to 2 months, for subacute cases it was between 2 to 12 months and for chronic *Brucellosis* it was above 12 months (3,15). In our study, the mean time from the onset of symptoms to diagnosis was 6 weeks. 78.87% (n=56) of the patients were acute and 21.12% (n=15) of the patients were subacute *Brucellosis*. In our study, the absence of chronic *Brucellosis* cases can be associated with the early diagnosis of patients.

Neurobrucellosis is usually seen in patients with late diagnosis and it has been reported in less than 5% of all *Brucellosis* patients in the literature (11,16,17). In our study, the absence of neurobrucellosis cases can be associated with the early diagnosis of patients who were still in the acute period of *Brucellosis*.

Genitourinary complications related to *Brucellosis* have rarely been reported as epididymo orchitis case reports. It presents with clinical symptoms in the form of scrotal pain and edema. (12,18,19). Similar to the literature, in our study, genitourinary complications related to *Brucellosis* was detected rarely (1.4% of patients).

Hematological and biochemical findings due to *Brucellosis* are not specific and not diagnostic. Indeed, they resolve with the treatment of the disease and usually does not require additional treatment (11,20-22). Similar to the literature, in our study, elevated ESR 83.09% (n=59), elevated CRP 36.21% (n=26) and elevated transaminase 80.28% (n=57) were detected (Table I).

In the literature, it has been reported that there are non-specific skin lesions such as petechiae, eczema, urticaria, papules and abscess in 0.7-17% of *Brucellosis* cases (17,23). In our study, findings of skin complaints were not observed other than petechia-purpura-ecchymosis due to thrombocytopenia. In our study, the absence of the skin lesion due to *Brucellosis* can be associated with the early diagnosis of patients who were in the acute or subacute period of *Brucellosis*.

Brucellosis can be confused with many diseases because it is a systemic infectious disease that can affect many organs and tissues and there are no diagnostic clinical or laboratory findings (1,3,5). In this study, it was determined that *Brucellosis* was confused with various disease (Table II).

Diagnosis of the disease is made by the bacterial culture and Wright agglutination test (1,3,14). However, bacteremia may not occur in all patients, so it is not always possible to produce bacteria (3,12,24). Therefore, serological tests play an important role in the diagnosis and Wright tube agglutination test is widely used in the serological diagnosis of *Brucellosis* (3,6,7,24,25). Polymerase chain reaction can be used for the rapid diagnosis of *Brucellosis*. However, it has not been routinely used because it is not standardized and it is expensive (3,12,16). Serological tests should be repeated in cases in which clinical findings strongly support *Brucellosis*. It is recommended that all family members of patients with *Brucellosis* should also be examined for the disease. In the literature, it was reported that the positivity rate of family anamnesis was 54.5% in *Brucellosis* cases (5). Similar to

the literature, in our study, family anamnesis (at least one person) was positive in 52.11% (n=37) of patients.

The *Brucellosis* can cause sometimes life-threatening complications such as spondylitis, infectious endocarditis and encephalitis. Complications usually occur due to late diagnosis and inadequate treatment (10,14). The absence of mortal complications in our study may be due to the early diagnosis of patients while still in the acute or subacute periods.

It should be kept in mind that the Wright agglutination test may produce false positive or false negative results. Therefore, although the Wright agglutination test may be negative, clinical findings and anamnesis are more important for diagnosis.

Study Limitations

The limitation of this study are the absence the long-term results of *Brucellosis*.

Conclusion

In our country where livestock farming is widespread, there is difficulty in the diagnosis of *Brucellosis* infections which is still a serious public health problem because of the lack of diagnostic clinical and laboratory findings. Although the early diagnosis and response to treatment of *Brucellosis* are very good, unfortunately, the late diagnosis and inadequate treatment may be causes of mortality and morbidity with serious complications. *Brucellosis*, which is an endemic disease common in our country, should be kept in mind in the diagnosis of child patients who have complaints such as fever, weakness, weight loss and especially joint pain, who present at a family health center or emergency unit.

Ethics

Ethics Committee Approval: This study was approved by Ethics Board of Mustafa Kemal University (approval number: 08/2018).

Informed Consent: All of the parents of the patients gave their informed consent prior to their child's inclusion in the study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

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

Conflict of Interest: None of the authors had conflict of interest.

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Case Report

Orofacial Crohn's Disease: A Case Report

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ABSTRACT

Crohn's disease (CD) is a chronic disease of the digestive system. It is characterized by lesions predominantly located in the small intestine and colon, although they may also occur in any segment of the gut, including the oral cavity. The involvement of oral mucosa in CD may be underreported, as up to 42% of pediatric patients with CD were found to have oral lesions after undergoing a thorough oral examination. Here, we present a case of CD in which the patient was referred to a dentist due to non-healing aphthous ulcers in the mouth. Our patient, a 16-year-old boy, was admitted to the dentistry clinic with swelling of the oral mucosa and the lips which had been ongoing for 3 months. The patient was referred to our department due to the non-response of the mucosal lesions to repeated cycles of medical treatment. Colonoscopy revealed a cobblestone appearance especially in the left colon, partly normal mucosa, and exudative ulcers. Biopsy samples showed increased inflammatory cell infiltration in the lamina propria and cryptitis in some of the crypts. A close collaboration between gastroenterologists and dentists is useful when addressing the diagnosis and appropriate management of these patients.

Keywords: Crohn's Disease, oral cavity, dentist

Introduction

Crohn's disease (CD) is a chronic disease of the digestive system. It is characterized by lesions predominantly located in the small intestine and colon, although they may also occur in any segment of the gut, including the oral cavity (1). Due to the prolonged course of the disease, diagnosis may be problematic; however, the findings of lesions in the oral mucosa may help to raise suspicion. The clinical spectrum of orofacial CD includes hyperplasia, cobble-stoning, ulceration of the buccal and gingival mucosa and swelling of the lips and face. The involvement of oral mucosa in CD may be underreported, as up to 42% of pediatric patients with CD were found to have oral lesions after undergoing a thorough oral examination (2). Here, we present a case of CD in which the patient was referred to a dentist due to non-healing aphthous ulcers in the mouth.

Case Report

Our patient, a 16-year-old boy, was admitted to the dentistry clinic with swelling of the oral mucosa and the lips which had been ongoing for 3 months. The patient was referred to our department due to the non-response of the mucosal lesions to repeated cycles of medical treatment. We were informed of the patient's history of anal fissure and diarrhea complaints which had occurred 1 year previously. There were no features in the medical history of the patient and his parents, and the patient had 2 healthy siblings. In physical examination, his weight was 55 kg (25-50 p), height 174 cm (50-75 p), cardiac pulse 96/minimum, and arterial blood pressure 120/80 mmHg. We observed a cobblestone appearance inside the mouth and swelling in the lips. His anal examination revealed two fissures. In the examinations for definitive diagnosis of inflammatory bowel diseases (IBD),

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sedimentation was found to be 60 mm/h, and C-reactive protein 3.5 mg/L. The patient's liver and kidney function tests were normal. Immunoglobulin G, A and M levels were 1.260 mg/dL, 390 mg/dL and 66.9 mg/dL, respectively. Whole blood count analyses were Hemoglobin: 10.4 gr/dL, hematocrit: 32.2%, Platelets: 304.000, Fe: 40 mg/dL and ferritin: 49 ng/mL. Upper and lower gastrointestinal system endoscopies were performed on the patient due to suspected IBD. Colonoscopy revealed a cobblestone appearance especially in the left colon, partly normal mucosa, and exudative ulcers. Biopsy samples showed increased inflammatory cell infiltration in the lamina propria and cryptitis in some of the crypts (Figure 1). The offer of Buccal biopsy was not consented by the teenage boy. Directed by the patient's medical history, physical examination, laboratory and biopsy findings, the patient was diagnosed with CD. The disease was extensive with PCDAI score of 30 and methylprednisolone treatment (60 mg/day) and mesalazine (40 mg/kg/d) were initiated. During an observation period of two weeks, the acute phase reactants of the patient normalized completely, the cobblestone appearance was restored and swelling receded. The dosage of methylprednisolone was decreased by 5 mg per week for four weeks, and 2 mg/kg/day of azathioprine was added to the treatment. The patient has been followed up with azathioprine maintenance and has been in clinical and laboratory remission for the last 18 months. Informed consent was obtained from the family.

Discussion

We report a case of a patient with CD presenting with cobblestone-like oral lesions. We confirmed the diagnosis of CD by performing a colonoscopy. Oral lesions immediately responded to high dose steroid treatment.

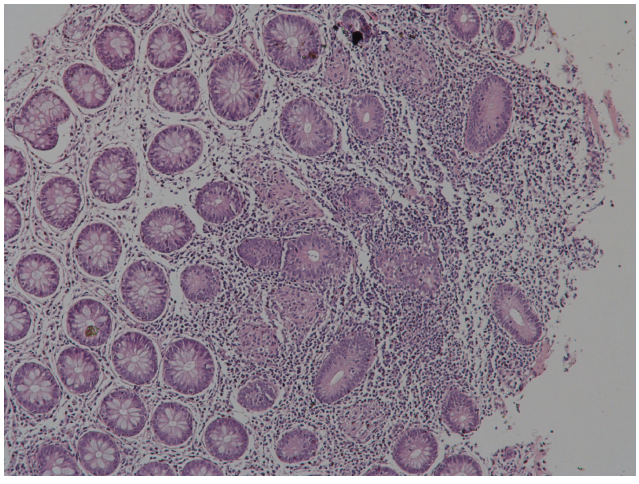

Figure 1. Histopathological examination (colon)
Explanation: Hematoxylin-eosin staining x10 magnification.
In lamina propria; non-caseating microgranulomas, increased infiltration of focal lymphocytes and cryptitis (focal active colitis)

A wide variety of disease-specific oral lesions have been described in patients with intestinal CD. These include swelling of the lips and buccal mucosa, cobble-stoning, mucogingivitis, deep linear ulceration or mucosal tags (3).

The prevalence of oral manifestations in patients with CD varies between 0% and 9% (4) in adults; however, it is more prevalent in children. In a prospective study of 48 children presenting with CD, clinicians accurately identified the presence of oral CD in less than 50% of children with disease-specific lesions.

Studies with larger sample sizes have also suggested that the finding of certain oral lesions may be indicative of CD, especially in children. In a prospective study conducted in Brazil comparing 62 CD patients with a control group, oral lesions were found in 14.5% of those patients with CD and in 9.6% of the control group, showing a low prevalence and an insignificant difference between the patients and controls (5). Bezerra et al. (6), assessing the oral mucosa of 100 adult patients with CD and ulcerative colitis for a period of 5 years, observed orofacial findings in only 7 patients, concluding that the association between CD and orofacial findings is not as strong as has been reported (6).

Some oral lesions have been postulated as possible indicators of the presence of CD. Rehberger et al. (4) described the case of a 20-year-old patient with painful intra-oral lesions. On endoscopy, extensive lesions of the gastrointestinal tract were seen, and biopsies confirmed the diagnosis of CD. In our case, we suspected CD due to non-healing painful oral lesions and confirmed the diagnosis by colonoscopic biopsies.

There is no evidence-based algorithm for the treatment of orofacial CD. Elemental diets appear to have variable outcomes. One case of facial and ileocolic CD showed improvement of the disease with total nutrition (7). Several case reports document remission of oral symptoms with topical or systemic steroids used in conjunction with aminosalicylic acid or mercaptopurine (8,9). There have also been several cases of orofacial CD refractory to steroids which were treated with infliximab (10). Since our patient had extensive disease, systemic corticosteroids were applied as a first line treatment according to the ECCO guidelines (11).

Many patients, particularly children, have involvement of the mouth when presenting with CD. Although usually subclinical, self-resolving and not requiring specific treatment, these disease-specific manifestations commonly harbor diagnostic material. Expert evaluation of the oral cavity is a

useful adjunct in patients presenting with suspected IBD. A close collaboration between gastroenterologists and dentists is useful when addressing the diagnosis and appropriate management of these patients.

Ethics

Informed Consent: Informed consent was obtained from the family.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.K., E.K.T., M.S., B.E.Y., F.Ç., Concept: M.K., E.K.T., M.S., B.E.Y., F.Ç., Design: M.K., E.K.T., M.S., B.E.Y., F.Ç., Data Collection or Processing: M.K., E.K.T., M.S., B.E.Y., F.Ç., Analysis or Interpretation: M.K., E.K.T., M.S., B.E.Y., F.Ç., Literature Search: M.K., E.K.T., M.S., B.E.Y., F.Ç., Writing: M.K., E.K.T., M.S., B.E.Y., F.Ç.

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

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Case Report

De Novo CHRNE Mutation: Congenital Myasthenic Syndrome

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ABSTRACT

Congenital myasthenic syndromes (CMS) are neuromuscular hereditary diseases with the symptoms of fatigue, weakness, ptosis, ophthalmoparesis and respiratory problems. This disease group is classified as CMS originating from the presynaptic region, synaptic gap and postsynaptic region according to the origin of the neuromuscular junction. Most of these patients are affected by receptor defects originating from the postsynaptic gap. Here, we present a case who was thirteen years old and had a CHRNE genotype p.Y124 *(c.372C> G) homozygous mutation, which is associated with weakness, low voice, ophthalmoparesis and frequent respiratory infection since birth. Our patient has been diagnosed with non-kinetic AChR deficiency and the case is important with the detection of a new mutation.

Keywords: Acetylcholine receptor deficiency, congenital myasthenic syndrome

Introduction

Congenital myasthenic syndromes (CMS) are genetic disorders of the neuromuscular junction that can be clinically variable. Sometimes the same mutation can cause different clinics and sometimes different mutations can cause the same clinics. As of present, mutations identified as disease-related have been shown in only 50% of patients with clinically diagnosed CMD (1). Beginning in childhood, specific autoantibodies being negative, detection of decrement responses or M responses in patients instead of myopathy are the indications of CMS in the patient (2).

Clinical findings vary according to mutation. The most common mutations are the mutations that cause defects in acetylcholine receptors (AchR). The most frequently observed mutation in these is the CHRNE mutation (3,4). The identification of these mutations is important for avoiding pyridostigmine, which may worsen myasthenic syndromes such as COLQ, DOK7 and slow-channel syndrome (1). It is also important to predict the prognosis and the mutation of the existing disease is likely to lead to a life-threatening condition.

A patient who has CHRNE de nova mutation was presented. He can be classified in the group "AchR deficiency-without a kinetic abnormality" group or primary AchR deficiency group.

Case Report

A 13-year-old male born to a second-degree consanguineous marriage presented with complaints of low eyelid, low voice crying and frequent respiratory tract infections since birth (Figure 1, 2). He had been diagnosed as CMS from the age of 8 months and used

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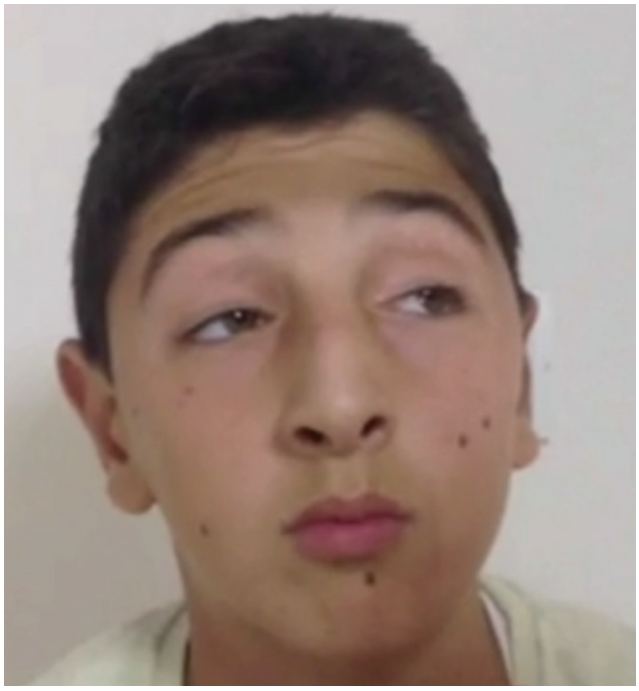

Figure 1. Bilateral ptosis

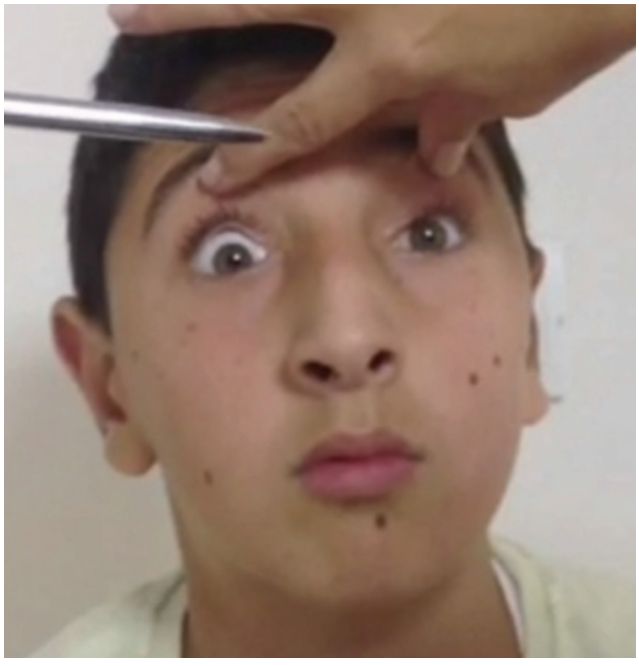

Figure 2. Bilateral ophthalmoparesis

pyridostigmine therapy and benefited. During this period, he had respiratory infections many times but he did not have a serious respiratory failure.

Neurologic examination revealed bilateral ptosis, outward and upward gaze limitation, thin and low voice, swallowing difficulty, normoactive deep tendon reflexes and 4/5 muscle strength. Skeletal anomaly and contracture were absent.

Muscle-specific tyrosine kinase and AChR antibody were negative. Electromyography (EMG) examination revealed 3 Hz decremental response at 3 and 5 Hz repetitive stimulation and there was no myopathy sign in needle EMG. Genetic analysis was performed for CMS, *de novo* p.Y124* (c.372C> G) homozygote mutation was also detected in the *CHRNE* gene. A mutation was not detected in the same region of the patient's parents. These findings were probable pathogenic for congenital myasthenic disease. The treatment of the patient continued with acetylcholine esterase inhibitors.

Informed consent was obtained from the patient's family.

Discussion

CMS, a hereditary disorder, is not characterized by autoimmunity. Lack of acetylcholine, kinetic anomalies, AchR deficiency, carrier protein anomalies or paucity of synaptic vesicle (2). Most complaints of patients start from birth. The defect may vary from severe respiratory failure to mild findings at birth, depending on the location (1-4). On physical examination, ptosis, limited eye movements, fatigable weakness, low crying, dysphagia and skeletal deformities can be observed (2). CMS are often misdiagnosed as congenital muscular dystrophies and mitochondrial myopathies because of their similar physical examination (1-4).

Weakness of diurnal rhythms in anamnesis, family history, recurrent infantile sibling death, frequent recurrent respiratory infections, age of onset of the disease and the progressive or stable course are helpful in diagnosing CMS.

For the diagnosis to be obtained in the decremental response in EMG, this response helps to narrow the differential recognition of presynaptic or post synaptic formation. Unlike autoimmune myasthenia in adult patients, repetitive stimulation for 5 minutes at 10 Hz in young children may be significant in terms of early and differential diagnosis (5). Even if CMS occurs clinically, genetic determination becomes important because of treatment differences.

In our patient, a postsynaptic decremental response was obtained, and this mutation was transmitted to the patient because the most common CMS in this group is associated with mutations in the *CHRNE* gene. Cases from our country showed that this mutation was detected in 15 of 43 patients (6).

Mutations in the *CHRNE* gene have been associated with CMS, which has a rapid channel kinetic abnormality and slow channel kinetic abnormality without AchR-kinetic abnormality (7-9).

However, consanguinity of the parents, the absence of similar disease histories in the family, and EMG findings excluded the autosomal dominant hereditary presynaptic region from the disease slow channel kinetic anomalies. The fast channel kinetic anomalies is a rapid and progressive disease. However, our patient's disease has been stable for years with only pyridostigmine treatment (2,4). Because of these, we thought that the fast channel kinetic anomalies was inappropriate for the diagnosis.

Consistent with the literature, our patient also had parents with a consanguineous marriage, stable clinical findings, intermittent swallowing difficulty and benefit from pyridostigmine (9-11).

With all these findings, our patient has complied with non-kinetic AChR deficiency and the case is important with the detection of a new mutation.

Since acetylcholine esterase inhibitors worsen the clinical condition in patients with mutations of DOK7, COLQ and slow-channel syndrome, differential diagnosis is very important in patients with CMS in order to conduct the correct therapy.

Although our patient responds to acetylcholine esterase inhibitors, in these cases 3-4-diaminopyridine and/or salbutamol may be tried in cases of treatment failure (1-3).

Ethics

Informed Consent: All of the parents of the patients gave their informed consent prior to their child's inclusion in the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.G., Concept: H.T., H.G.T., S.Y., Design: S.Y., H.G.T., Data Collection or Processing: G.A., H.G.T., Analysis or Interpretation: S.G., H.T., Literature Search: H.G.T., Writing: H.G.T.

Conflict of Interest: None of the authors had conflict of interest.

Financial Disclosure: The authors declared that this study received no financial support.

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Case Report

Endotracheal N-acetylcysteine for Atelectasis in Neonatal Pneumonia

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ABSTRACT

Although there is no gold standard therapy in the treatment of atelectasis in newborns, surfactant therapy, inhaled mucolytic agents, recombinant human deoxyribonuclease, positive pressure mechanical ventilation, postural changes and drainage can be used. However, N-acetylcysteine (NAC), via endo-bronchoscopy, is rarely used to break the disulfide bonds in the mucus. It is a cheap and readily available treatment to apply. Here, we present a newborn with neonatal pneumonia to whom we instilled NAC thorough an endotracheal tube to resolve right lung total atelectasis. The atelectasis responded to instillation quickly and successfully. We are presenting this case in order to suggest a novel effective treatment modality for already intubated newborns with atelectasis. This case also represents the first successful treatment case in the newborn period.

Keywords: Atelectasis, N-acetylcysteine lavage, newborn

Introduction

Inflammatory response in the airway causes necrosis and loss of the respiratory epithelium. The result of tissue edema and mucus production with the addition of air causes thick mucus plugs. This can disrupt the normal function of the airways. Full mucus plug blockages lead to atelectasis, whereas partial blockage causes air trapping. In neonatal intensive care, there are limited treatment options for atelectasis. This lack of options in resistant atelectasis has led to the search for safe and effective novel treatment modalities. Here, we report an atelectasis which occurred in a premature neonate which resolved quickly after N-acetylcysteine (NAC) instillation through an endotracheal tube. We report the case and similar literature findings since this treatment modality might be a novel treatment for neonatal atelectasis in intensive care units.

Case Report

A premature baby was born after 34 weeks of gestation. He weighed 1.785 kg and was born to a non-consanguineous marriage. The antenatal follow-up was normal. A history of cystic fibrosis was not obtained. Physical examination revealed respiratory distress. He was hospitalized in the neonatal intensive care unit. During the next 48 hours, chest retractions and oxygen demand increased despite nasal positive pressure support. We started ampicillin with sulbactam and amikacin for the treatment of neonatal pneumonia and early onset sepsis. However, the patient developed hypercapnia and required endotracheal intubation. During mechanical ventilation, C-reactive protein increased and antibacterial therapy was substituted for teicoplanin and meropenem. Intravenous immunoglobulin was given for sepsis. On postnatal day 9,

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we observed increased respiratory effort and substantial retractions. Chest examination showed decreased respiratory sounds over the right lung. Radiography demonstrated total loss of volume in the relevant lung with the trachea and heart displaced to the right (Figure 1). The patient needed postural drainage for the atelectasis. The mediastinal shift to the right did not respond to effective chest therapy. After parental consent, we tried NAC (Asist® for parenteral use) 200 mg-1 mL mixed with 3 mL of 0.9% saline (1). One mL of a total of 4 mL was introduced each time through a tracheal tube and the patient was aerated and oxygenated via bag and mask ventilation for 1 minute. We positioned the patient's head to the left, aiming the solution to the right main bronchus. The patient was also positioned to the right lateral side during the instillation. After four 4-hour-apart instillations, we observed increased sounds over the right lung. The need for oxygen also decreased. At the end of 12 hours from the first instillation, near total resolution of the atelectasis was seen in chest X-ray (Figure 2).

The patient was extubated 24 hours following the procedure. Antibacterial treatment was completed in 14 days. He was discharged on postnatal day 30. The repeat sweat test was negative.

Discussion

Pulmonary atelectasis is defined as a partial or total collapse or incomplete expansion of the alveolar spaces. One factor leading to atelectasis results from an obstruction of the airways by an abundant, thick and sticky mucus (2). Mucus is a non-homogeneous, viscoelastic fluid and is composed of glycoproteins predominantly linked by disulfide bonds, proteins, lipids and water. Another factor for atelectasis is the poor clearance of inflammatory debris that occludes the lumen of the airways. Edema of the bronchial wall and smooth muscle constriction are additive factors leading to complete obstruction. A third factor for atelectasis is surfactant deficiency or dysfunction, which causes increased alveolar surface tension with subsequent diffuse atelectasis.

Atelectasis is a severe problem in many newborn babies with pulmonary infections, surfactant insufficiencies or ventilator support (3). The most common cause during the neonatal period is hyaline membrane disease. Pneumonia or pulmonary edema by way of secondary surfactant insufficiency are the other causes (4).

Treatment options for atelectasis such as chest physiotherapy, inhaled bronchodilators, steroids, nebulized

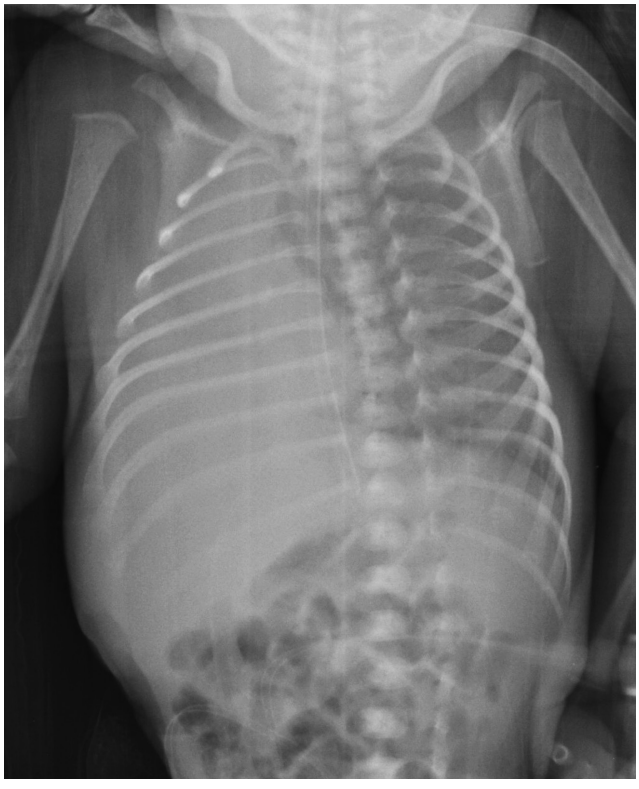

Figure 1. Chest X-ray before N-acetylcysteine instillation. Note the collapse of the right lung with right mediastinal shift

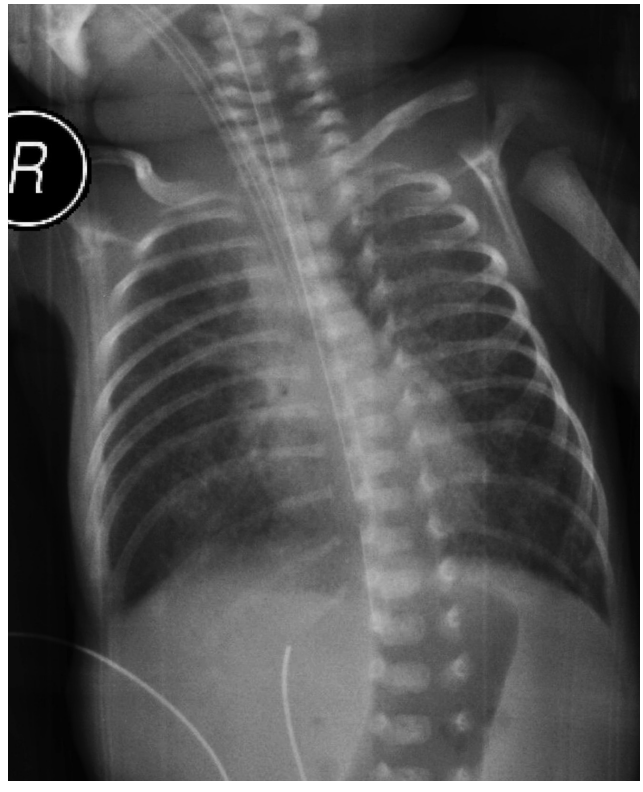

Figure 2. Chest X-ray after 12 hours of N-acetylcysteine instillation. Near-total resolution or expansion of the right lung was observed

sodium chloride (NaCl 0.9%) and recombinant human deoxyribonuclease (DNase) have been developed but their efficiency has not been proven in the neonatal period. The treatment objective in atelectasis is mainly focused on eliminating the viscoelastic plugs within the airways (2).

Mucolysis can be achieved either through physical intervention, such as high frequency oscillation, or by biochemical or pharmacologic agents, such as NAC or DNase (5,6). Mucolytic agent NAC with inherent anti-inflammatory properties in experimental models reduces the mucus viscosity and elasticity by breaking disulfide bonds (7,8).

Human DNase has also been used to reduce the viscosity of secretions in acute and chronic respiratory conditions. DNase application via bronchoscopy for mucolysis in the treatment of atelectasis in preterm and term neonates has been reported (2,3,9,10). We preferred NAC as the mucolytic agent in our patient for several reasons. The first factor is that its use is feasible. Another factor is that it is easily affordable. To our knowledge, there are no studies comparing the efficacy of NAC to DNase or saline but our research has shown that it has great potential in the treatment of newborns. The drug was applied to a newborn who had already been intubated with a tracheal tube, so no further invasive measures were needed for this alternative treatment.

In animal models, NAC improved oxygenation, reduced lung edema, decreased polymorphonuclear leukocytes in bronchoalveolar lavage fluid, diminished peroxidation and meconium-induced airway reactivity compared with untreated animals (11).

In accordance with our observation, a previous case study also observed a successful expansion of an atelectatic lung in a 35-year-old women with pneumonia in whom NAC in 3 ml of physiologic saline was instilled through an endotracheal tube (12). In another case report, a 2-month-old male infant presenting with atelectasis, severe respiratory failure and pulmonary hypertension, and requiring extracorporeal membrane oxygenation responded well to repeated NAC instillations with bronchoscopy (9). Our newborn patient, the youngest reported in English literature, had a near total collapse or atelectasis in the right lung. After one hour of instillation through an endotracheal tube, clinical improvement occurred. There was near-complete resolution of the right lung on chest X-ray after 12 hours of instillation.

Bibi et al. (13) previously reported such side effects as bradycardia, cyanosis and increased airway resistance in preterm babies who had received intratracheal 5% NAC every 4 hours. The findings of the authors did not support the use of NAC as mucolytic for extremely preterm neonates with chronic pulmonary disease. The absence of the desired effects of NAC in that study conducted in preterm infants with chronic pathology characterized by alveolar and vascular insufficiency in addition to fibrosis as opposed to our case which was an acute pathology with neonatal pneumonia in a late preterm infant is an important difference.

On these grounds, we suggest that NAC instillation through tracheal tube for already intubated newborns can be considered as an effective, easy and novel treatment modality for atelectasis. This case is unique since there are no similar reports in the literature for this particular age group. Our case has demonstrated the need for further controlled studies in which similar implementations of NAC are used.

Ethics

Informed Consent: Permission and consent was obtained from parents.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.D., H.İ.A., S.A., Concept: M.D., H.İ.A., Design: M.D., H.İ.A., Data Collection or Processing: M.D., H.İ.A., S.A., Analysis or Interpretation: M.D., H.İ.A., S.A., Literature Search: M.D., H.İ.A., Writing: M.D., H.İ.A.

Conflict of Interest: The authors have no conflicts of interest relevant to this article to disclose.

Financial Disclosure: The authors have no financial relationships relevant to this article to disclose.

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Oya Halıcıoğlu
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Saadet Mahmutoğlu
Sadık Akşit
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Sanem Yılmaz
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İlk adımdan ilk başarılara

BEXSERO, MenB* aşılamasında 2. aydan itibaren endike olan tek aşıdır.[1,2]

BEXSERO
Meningokok Grup B Aşısı
(rekombinant, adsorbe)

Dünya genelinde **30 milyondan fazla doz** dağıtılmıştır.[3]

Dünya genelinde **41'den fazla ülkede** ruhsatlıdır.[4]

BEXSERO: Geniş bir popülasyonda koruma sağlamaya yardımcı olur[1]

Geniş yaş aralığı

BEXSERO,
2. aydan itibaren kullanılabilir.[1]

Geniş kapsayıcılık

BEXSERO,
4 farklı antijeni hedefler: fHbp, NadA, PorA ve NHBA[1,5-8]

Gerçek dünya deneyimi

BEXSERO,
ulusal bağışıklama programlarında bebekler için kullanılmaktadır.[9-11]

Esnek doz seçenekleri

BEXSERO,
rutin aşılama ziyaretlerine uygun çeşitli program seçenekleri sunar.[1]

*Meningokokal hastalık, serogrup B.

Referanslar: 1. BEXSERO KÜB, Eylül 2018. **2.** Pfizer Ltd. Trumenba, European publc assessment report, Annex I: Summary of product characterstcs. EMA; June 2017. Avalable from: <http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Informaton/human/004051/WC500228995.pdf>. Accessed June 2017. **3.** Data on file;2017N320400_04;1-2 **4.** DOF 2016N297580_01 Bexsero countries commercialized-coversheet-18Jul2018. **5.** Biagini M, Spinsanti M, De Angelis G, et al. Expression of factor H binding protein in meningococcal strains can vary at least 15-fold and is genetically determined. Proc Natl Acad Sci USA. 2016;113:2714-2719. **6.** Livorsi DJ, Stenehjem E, Stephens DS. Virulence factors of gram-negative bacteria in sepsis with a focus on Neisseria meningitidis. Contrib Microbiol. 2011; 17:31–47. **7.** Hao W, Ma JH, Warren K, et al. Extensive genomic variation within clonal complexes of Neisseria meningitidis. Genome Biol Evol. 2011;3:1406–1418. **8.** Vogel U, Taha M-K, Vasquez JA, et al. Predicted strain coverage of a meningococcal multicomponent vaccine (4CMenB) in Europe: a qualitative and quantitative assessment. Lancet Infect Dis. 2013;13:416-425. **9.** Meningococcal B. National Immunisation Office website. http://hse.ie/eng/health/immunisation/hcpinfo/OtherVaccines/meningococcalb/. Accessed April 3, 2017. **10.** Piano Nazionale Prevenzione Vaccinale PNPV 2017-2019. Ministero della salute website. http://www.salute.gov.it/imgs/C_17_pubblicazioni_2571_allegato.pdf. Accessed April 3, 2017. **11.** Guidance: Meningococcal B vaccine: JCVI position statement. Gov.UK website. https://www gov.uk/government/publications/meningococcal-b-vaccine-jcvi-position-statement. Accessed February 13, 2017.

BEXSERO Kısa Ürün Bilgisi
BEXSERO 0.5 mL IM Enjeksiyonluk Süspansiyon İçeren Kullanıma Hazır Enjektör Çok bileşenli Meningokok grup B Aşısı (rekombinant, adsorbe) **Etkin maddeler:** Bir doz (0.5 mL) şu etkin maddeleri içerir: Rekombinant Neisseria meningitidis grup B NHBA füzyon proteini 50 mikrogram, rekombinant Neisseria meningitidis grup B NadA proteini 50 mikrogram, rekombinant Neisseria meningitidis grup B fHbp füzyon proteini 50 mikrogram, PorA P1.4 içeren toplam protein miktarı olarak ölçülen Neisseria meningitidis grup B suşu NZ98/254'ten dış membran vezikülleri (OMV) 25 mikrogram. **Yardımcı maddeler:** Sodyum klorür, histidin, sükroz, enjeksiyonluk su, alüminyum hidroksit. **Farmasötik form:** Enjeksiyonluk süspansiyon içeren kullanıma hazır enjektör. Beyaz, opak sıvı süspansiyon. **Terapötik endikasyonlar:** BEXSERO, 2 ay ve üzeri yaştaki kişilerin, Neisseria meningitidis grup B'nin neden olduğu invazif meningokok hastalığına karşı aktif bağışıklanması için endikedir. İnvazif hastalığın farklı yaş gruplarındaki etkisi ile birlikte grup B suşlarının farklı coğrafi bölgelerdeki antijen çeşitliliği de aşılama sırasında göz önünde bulundurulmalıdır. **Pozoloji ve uygulama şekli:** 2 ila 5 aylık bebekler için aşı programı: her biri 0.5 ml'lik üç primer doz (ilk doz 2 aylıkken verilir), primer dozlar arasındaki süre en az 1 ay olmalıdır ve 12 ay ile 23 ay arasında bir rapel doz uygulanır. 6 ila 11 aylık aşılanmamış bebekler için aşı programı: her biri 0.5 ml'lik iki primer doz, primer dozlar arasındaki süre en az 2 ay olmalıdır ve primer seri ile rapel doz arasında 2 aylık süre bırakılarak yaşamın 2. yılında bir rapel doz uygulanır. 12 ila 23 aylık aşılanmamış bebekler için aşı programı: her biri 0.5 ml'lik iki primer doz, primer dozlar arasındaki süre en az 2 ay olmalıdır ve primer seri ile rapel doz arasında 12-23 aylık süre bırakılarak bir rapel doz uygulanır. 2 ila 10 yaş çocuklar için aşı programı: her biri 0.5 ml'lik iki primer doz, primer dozlar arasındaki süre en az 2 ay olmalıdır ve rapel doz için gereklilik belirlenmemiştir. 2 ila 10 yaş çocuklar için aşı programı: her biri 0.5 ml'lik iki primer doz, primer dozlar arasındaki süre en az 2 ay olmalıdır ve rapel doz için gereklilik belirlenmemiştir. Adölesanlar (11 yaşından itibaren) ve erişkinler için aşı programı: her biri 0.5 ml'lik iki primer doz, primer dozlar arasındaki süre en az 1 ay olmalıdır ve rapel doz için gereklilik belirlenmemiştir (50 yaşın üzerindeki erişkinlerde veri mevcut değildir). **Uygulama şekli:** Aşı, tercihen bebeklerde uyluğun anterolateral bölgesine ve daha büyük hastalarda üst kolun deltoid kası bölgesine derin intramüsküler enjeksiyon şeklinde yapılmalıdır. **Kontrendikasyonlar:** Bu tıbbi ürün etkin maddeye ya da yardımcı maddelere karşı bilinen aşırı duyarlılığı olan kişiler kullanmamalıdır. **Özel kullanım uyarıları ve önlemleri:** BEXSERO uygulaması akut şiddetli ateşli hastalık geçiren kişilerde ertelenmelidir. Bununla birlikte, soğuk algınlığı gibi minör enfeksiyon varlığında aşılama ertelenmemelidir. İntravasküler yolla enjekte edilmemelidir. BEXSERO trombositopenisi ve kanama bozuklukları olan kişilere intramüsküler uygulama kontrendike olacağından uygulanmamalıdır. Bu kişilere ancak potansiyel yararın risklerden fazla olması durumunda uygulanabilir. BEXSERO'nun dolaşımdaki tüm meningokok grup B suşlarına karşı koruma sağlaması beklenemez. Birçok aşıda olduğu gibi, sağlık mesleği mensupları, bebekler ve çocukların (2 yaş altı) aşılanmasından sonra vücut sıcaklığında olabilecek yükselmelerin bilincinde olmalıdır. Aşılama zamanında ve aşılamadan kısa bir süre sonra profilaktik antipiretik uygulaması, aşılama sonrası febril reaksiyonların insidansını ve şiddetini azaltabilir. Antipiretik ilaçlara, bebekler ve çocuklara (2 yaş altı) yönelik yerel kılavuzlar doğrultusunda başlanmalıdır. BEXSERO'nun 50 yaş ve üzeri kişilerde kullanımına ilişkin veri bulunmamaktadır. Çok prematüre bebekler (gebeliğin 28. haftası ve öncesinde doğanlar) ve özellikle solunum sistemi gelişimi eksikliği hikayesi olanlarda primer bağışıklama serilerinin uygulanmasında potansiyel apne riskine karşı 48-72 saat solunum sisteminin izlenmesi gerekmektedir. Bu grup bebekte aşılamanın yararı yüksek olduğundan, aşılama alıkonmamalı ve ertelenmemelidir. Enjektörün uç kapağı doğal kauçuk lateks içerebilir. Latekse bağlı alerjik reaksiyon gelişme riski çok düşük olmakla birlikte, latekse karşı hipersensitivite öyküsü bilinmeyen kişilerde risk yarar oranı göz önünde bulundurulmalıdır. **Diğer tıbbi ürünler ile etkileşimler ve diğer etkileşim şekilleri:** BEXSERO, parantez içerisinde belirtilen aşı antijenlerinin herhangi birinin monovalan ya da kombinasyon şeklindeki aşıları ile (difteri, tetanoz, aselüler boğmaca, Haemophilus influenzae tip b, inaktif çocuk felci aşısı, hepatit B, 7-valanlı konjüge pnömokok, kızamık, kabakulak, kızamıkçık ve su çiçeği ve meningokok grup C-CRM konjuge aşısı) eşzamanlı olarak uygulanabilir. BEXSERO ile burada listelenen diğer aşıların eş zamanlı uygulanması sonrasında daha sık ortaya çıkan ateş, enjeksiyon yerinde hassasiyet, yeme alışkanlıklarında değişiklik ve iritasyon nedeniyle mümkün olduğu durumlarda aşılamaların farklı zamanlarda yapılması düşünülebilir. Profilaktik parasetamol kullanımı, BEXSERO ya da rutin aşılara immünojenisiteyi etkilemeksizin ateş insidansını ve şiddetini azaltır. Parasetamol dışında diğer antipiretiklerin immün yanıt üzerindeki etkisi çalışılmamıştır. **Gebelik ve laktasyon: Gebelik kategorisi: B. Gebelik dönemi:** Gebeliklerde maruz kalmaya ilişkin klinik veri mevcut değildir. Hayvanlar üzerinde yapılan çalışmalar, gebelik / embriyonal / fetal gelişim / doğum ya da doğum sonrası gelişim ile ilgili olarak doğrudan ya da dolaylı zararlı etkiler olduğunu göstermemektedir **Laktasyon dönemi:** Emzirme sırasında kadınlar ve çocuklarda aşının güvenilliği ile ilgili veri mevcut değildir. **İstenmeyen etkiler:** Yeme bozuklukları, uykulu olma, alışılmışın dışında ağlama, baş ağrısı, ishal, kusma, döküntü, artralji, ateş, irritabilite, enjeksiyon bölgesinde eritem, enjeksiyon bölgesinde şişlik, enjeksiyon bölgesinde sertlik, egzema, ürtiker, deri renginde solukluk, Kawasaki sendromu, hipotonik-hiporesponsif atak, nöbetler, alerjik reaksiyonlar. **Doz aşımı:** Doz aşımı deneyimi sınırlıdır. Doz aşımı durumunda tüm yaşamsal fonksiyonların izlemi ve olası semptomatik tedavi önerilmektedir. **Raf ömrü:** 36 ay. **Saklamaya yönelik özel tedbirler:** 2-8°C arası sıcaklıklarda (buzdolabında) saklayınız. Dondurmayınız. Işıktan koruyunuz. **Ambalajın niteliği ve içeriği:** Piston tıpa (Tip I bromobütil kauçuk) ve koruyucu uç kapaklı (Tip II kauçuk), iğneli veya iğnesiz kullanıma hazır dolu enjektör (Tip I cam) içinde 0.5 mL süspansiyon. **Ruhsat sahibi:** GlaxoSmithKline ilaçları Sanayi ve Ticaret A.Ş. Büyükdere Cad. No:173 1. Levent Plaza B Blok 34394, 1.Levent / İSTANBUL **Ruhsat numarası:** 2018/470. **Ruhsat tarihi:** 06.09.2018 **Fiyatı:** 19 Şubat 2019 itibari ile KDV dahil perakende satış fiyatı 403,92 TL. **Reçete ile satılır.** GSK ürünleri ile ilgili advers olayları GSK'ya doğrudan e-posta (ist_tr_safety@gsk.com) ve telefon aracılığı ile (444 54 75) veya T.C. Sağlık Bakanlığı, Türkiye İlaç ve Tıbbi Cihaz Kurumu, TÜFAM'a (Türkiye Farmakovijilans Merkezi: e-posta: tufam@titck.gov.tr; faks: 0312 218 35 99; tel: 0312 218 30 00) iletebilirsiniz. Daha geniş bilgi için firmamıza başvurunuz. GlaxoSmithKline İlaçları San. ve Tic. A.Ş. Büyükdere Cad. 1. Levent Plaza B Blok No: 173 1. Levent 34394 İSTANBUL Tel: 0212 339 44 00 www.gsk.com.tr. **KÜB özeti onay kodu:** PI-0234

PM-TR-BEX-ADVT-190001

▼ Bu ilaç ek izlemeye tabidir. Bu üçgen yeni güvenlilik bilgisinin hızlı olarak belirlenmesini sağlayacaktır. Sağlık mesleği mensuplarının şüpheli advers reaksiyonlarını bildirmeleri beklenmektedir. Raporlama yapılması, ilacın yarar/risk dengesinin sürekli olarak izlenmesine olanak sağlamaktadır. Herhangi bir şüpheli advers reaksiyonu Türkiye Farmakovijilans Merkezi (TÜFAM)'ne (www.titck.gov.tr; e- posta: tufam@titck.gov.tr; tel: 0 800 314 00 08; faks: 0 312 218 35 99) ve/veya GSK Ürün Güvenliği Departmanı'na doğrudan e-posta (ist_tr_safety@gsk.com) ve telefon aracılığı ile (444 5 475) bildirmeniz gerekmektedir.

DAHA GENİŞ BİLGİ VE KISA ÜRÜN BİLGİSİ İÇİN FİRMAMIZA BAŞVURUNUZ.
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