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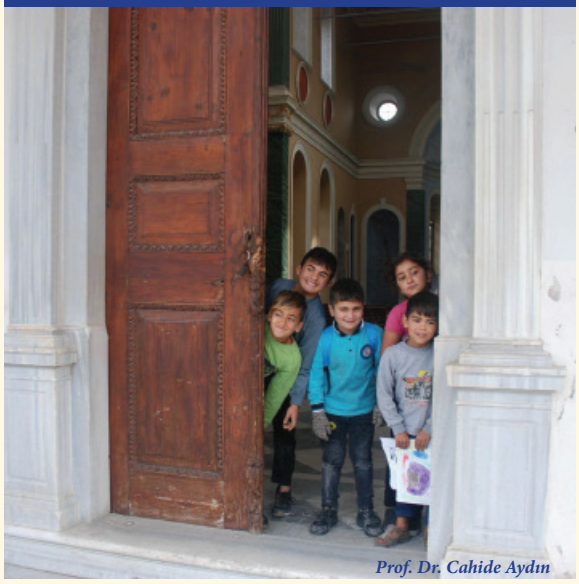

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PRISMA statement of preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med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

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al., for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org/);

STROBE statement, a checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/);

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Abbreviations: Abbreviations should be defined at first mention and used consistently thereafter. Internationally accepted abbreviations should be used; refer to scientific writing guides as necessary.

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To ensure controllability of the research findings, the study design, study sample, and the methodological approaches and applications should be explained and their sources should be presented.

The "p" value defined as the limit of significance along with appropriate indicators of measurement error and uncertainty (confidence interval, etc.) should be specified. Statistical terms, abbreviations and symbols used in the article should be described and the software used should be defined. Statistical terminology (random, significant, correlation, etc.) should not be used in non-statistical contexts.

All results of data and analysis should be presented in the Results section as tables, figures and graphics; biostatistical methods used and application details should be presented in the Materials and Methods section or under a separate title.

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Results: The detailed results of the study should be given and the statistical significance level should be indicated.

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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Materials and Methods: The study plan should be clearly described, indicating whether the study is randomized or not, whether it is retrospective or prospective, the number of trials, the characteristics, and the statistical methods used.

Results: The results of the study should be stated, with tables/figures given in numerical order; the results should be evaluated according to the statistical analysis methods applied. See General Guidelines for details about the preparation of visual material.

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Study Limitations: Limitations of the study should be discussed. In addition, an evaluation of the implications of the obtained findings/results for future research should be outlined.

Conclusion: The conclusion of the study should be highlighted.

Acknowledgements: Any technical or financial support or editorial contributions (statistical analysis, English evaluation) towards the study should appear at the end of the article.

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Review articles can address any aspect of clinical or laboratory pediatry. Review articles must provide critical analyses of contemporary evidence and provide directions for future research. **The journal only accepts and publishes invited reviews.** Before sending a review, discussion with the editor is recommended.

Reviews articles analyze topics in depth, independently and objectively. The first chapter should include the title in English, an unstructured summary and key words. Source of all citations should be indicated. The entire text should not exceed 18 pages (A4, formatted as specified above

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The
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Official Journal of Ege University Children's Hospital

Contents

Original Articles

Case Reports

The
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Editorial

Dear Readers,

We are happy to welcome you to the last issue of The Journal of Pediatric Research in 2018.

We present to you 14 articles including 7 research articles and 7 case reports in the fourth issue of 2018. These articles have been written in different disciplines. The first research we present is "Seasonal variation of vitamin D via several parameters in adolescents". This article emphasizes the importance of vitamin D. The next research article is about the oral and dental health status in hemophilic children and adolescents. We believe that the other research articles in this issue will also contribute to the literature. In addition, the case reports in this issue are rare and interesting cases in the literature such as "Bannayan-Riley-Ruvalcaba syndrome", "Stenotrophomonas maltophilia sepsis presenting with perianal cellulitis" and "Renal lymphangiectasia". The number of articles sent to our journal within the last year has increased. All articles are carefully evaluated by the editorial board and we work with great effort. As a result of this effort, we hope The Journal of Pediatric Research is to be in the Pubmed and SCI index in the next year.

We would like to acknowledge the members of our editorial board, reviewers, authors and Galenos Publishing House for preparing the fourth issue of 2018. We look forward to seeing your scientific research articles in our future issues.

We hope you benefit from these articles.

Best wishes and a happy new year.

Feyza Koç, MD, Associate Professor of Pediatrics,
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Original Article

Seasonal Variation of Vitamin D via Several Parameters in Adolescents

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ABSTRACT

Aim: Vitamin D in adolescents reveals that subclinical vitamin D deficiency is continuously increasing worldwide. The aim of this study was to investigate the prevalence of vitamin D and subclinical vitamin D deficiency and risk factors among adolescents in the summer and winter seasons in İzmir.

Materials and Methods: The medical records of 90 adolescents were reviewed regarding their vitamin D status in the summer and winter seasons. Blood samples were obtained from 90 adolescents at the end of summer and the end of winter. These samples were assessed for calcium (Ca++), phosphorus, magnesium (Mg), parathyroid hormone, alkaline phosphatase and 25-hydroxyvitamin D concentrations. The subjects were divided into two groups; the first group consisted of the patients who were assessed for vitamin D levels and the other laboratory measurements at the end of winter (n=46), the second group consisted of the patients who were assessed for the same laboratory features at the end of summer (n=44). The two groups were compared in terms of demographic, clinical and laboratory characteristics.

Results: Among the 90 patients enrolled in the study, 41 (45.5%) were males and 49 (54.5%) were females. The median age was 11±4 years. Vitamin D deficiency percentages of the study group for the end of the winter period was 60.8% and for the end of the summer period was 6.8% but this was not statistically significant. Vitamin D insufficiency percentages of the winter group were higher than the summer group (93.2% vs. 39.2%, p>0.05). There were no differences between the groups in terms of laboratory findings concerning Ca, Mg and the other bone parameters.

Conclusion: Contrary to the expected, we did not detect a seasonal difference in vitamin D levels in adolescents. Although laboratory findings were not found to be statistically significant in terms of vitamin D levels, we can state that the level of vitamin D in the winter season might be lower than the summer season. Therefore, it should be kept in mind that vitamin D insufficiency is more frequent at the end of the winter season and seasonal differences in the adolescent population should be considered during measurement.

Keywords: Vitamin D, seasonal variation, adolescents

Introduction

Vitamin D plays a role in the growth of bone and bone mineralization. The bone developments during adolescence accelerate in a short period of time. This increased metabolic demand suggests an increased need for calcium (Ca) and vitamin D. Low vitamin D and Ca intake, together with dark skin pigmentation and lack of sunlight exposure may predispose this age-group to nutritional rickets. Vitamin D plays not only an essential role in maintaining healthy bone growth but also in reducing the risk of chronic diseases such as autoimmune diseases, malignancies, cardiovascular and infectious diseases (1). Vitamin D deficiency is a common entity in children and adolescents who are dark skinned and on vegetarian or unusual diets. The usage of anticonvulsant or antiretroviral medications, malabsorptive conditions, residence at higher latitudes, the winter season and other causes of low sun exposure are also associated with Vitamin D deficiency (2-4). Standards for defining vitamin D status in healthy children and adolescents are based on the 2016

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Global Consensus recommendations and upon serum concentrations of 25-hydroxyvitamin D (25-OHD): Vitamin D sufficiency is defined as 20 to 100 ng/mL (50 to 250 nmol/L), Vitamin D insufficiency is defined as 12 to 20 ng/mL (30 to 50 nmol/L), and Vitamin D deficiency is defined as <12 ng/mL (<30 nmol/L) (5,6). Due to the fact that the prevalence of vitamin D deficiency or insufficiency might be changeable with respect to different countries, subpopulations, different ethnic and socio-economic features, the exact prevalence is not clear. However, reports have stated that the overall prevalence of vitamin D deficiency in the pediatric age range is about 15 percent (4,7,8).

Studies regarding vitamin D in adolescents have revealed that subclinical vitamin D deficiency is continuously increasing worldwide. Many factors appear to be important in this pathogenesis such as obesity, living in temperate climates, lack of sunlight exposure, darkly pigmented skin and also social and religious customs that prevent sunlight exposure. However, even in sunshine rich countries, vitamin D deficiency can develop. Manios et al. (9) reported that sub-populations at highest risk are girls in urban/semi-urban areas during the spring months, thus indicating the need for effective initiatives to support adequate vitamin D levels in these population groups.

Subclinical vitamin D deficiency (Vitamin D insufficiency) is characterized by an inadequate vitamin D level with non-specific clinical symptoms. Because these cases are either under diagnosed or missed, subclinical vitamin D deficiency is one of the most common undiagnosed medical conditions in the world (10).

The diagnosis of vitamin D deficiency is based on a combination of clinical features (which may include bone pain and tenderness, carpopedal spasms, diffuse limb pains, deformities of the lower limbs and generalized weakness, fractures, etc.), laboratory results, and radiologic findings. Those patients with nutritional osteomalacia have a very low serum 25-OHD [<10 ng/mL (25 nmol/L)], low to low-normal serum Ca and phosphate, and high parathyroid hormone (PTH) and alkaline phosphatase (ALP) (both total and bone-specific) levels. Radiographic evidence shows a widening of the growth plate with impaired mineralization.

The studies have reported that the risk of vitamin D deficiency could be related to many risk factors. The current study aimed to investigate the frequency of vitamin D insufficiency and vitamin D deficiency and the risk factors among adolescents in the summer and winter seasons in İzmir, which is located in the west of Turkey and is a sunshine rich city.

Materials and Methods

Study Group

We evaluated 90 adolescents (aged between 10-18 years) who presented for various reasons at the outpatient clinic of Ege University Children's Hospital between July and September 2011 and between January and March in 2012. Those patients with chronic illness or use of medications known of affect bone metabolism were excluded. The protocol for the study was approved by the Ethical Committee and informed consent was obtained from the parents or guardians of all eligible children.

The subjects were divided into two groups; the first group consisted of those patients who were assessed for vitamin D levels and the other laboratory measurements at the end of winter, the second group consisted of those patients who were assessed for the same laboratory features at the end of summer. Demographic variables including age, sex, ethnicity, height and weight were recorded on a standard case report form for all patients. All of the participants were questioned about their nutritional intake (Ca and vitamin D) and physical activity (hours per week and time engaged in outdoor activities). The questionnaires included an assessment of Ca and vitamin D intake (dietary and supplements). Daily acidic beverage consumption was also assessed. The outdoor physical activity and dressing styles for female patients were determined as normal or covered completely with traditional clothing. Daily sun exposure and sunscreen usage were evaluated in patients. The two groups were compared in terms of demographic, clinical and laboratory characteristics.

Laboratory Investigations

Blood samples were obtained from 44 adolescents at the end of summer and 46 at the end of winter. Samples were assessed for $Ca^{++,}$ phosphorus (P), magnesium (Mg), PTH, ALP and 25-OHD concentrations. Serum Ca, P and ALP were measured spectrophotometrically. Total 25-OHD levels in the sera were measured by a chemiluminescence immunoassay method (Diasorin Inc, Stillwater, MN). This assay uses an antibody that is able to detect both forms of 25-OHD (D2 and D3). The normal range for PTH is 10-55 pg/mL.

The patients were divided into 3 diagnostic categories according to their serum 25-OHD concentrations: Vitamin D insufficiency 15-20 ng/mL; Vitamin D deficiency 15 ng/mL or less; severe Vitamin D deficiency 8 ng/mL or less. The definition of Vitamin D deficiency; serum 25-OHD levels of 15 ng/mL or less had elevated serum PTH concentrations. Subclinical vitamin D deficiency is characterized by an inadequate vitamin D level without overt specific signs and symptoms referred to altered mineral homeostasis.

Statistical Analysis

Statistical analyses were performed using IBM SPSS version 21.0 for personal computers (Chicago, IL, USA). The subjects were divided into two groups: the first group was those patients who were assessed for vitamin D levels and the other laboratory measurements at the end of winter (n=46), the second group was those patients who were assessed for the same laboratory features at the end of

summer (n=44). The Shapiro-Wilk test was used to check the normality assumption of the continuous variables. χ^2 test was used to compare categorical data. In cases of non-normally distributed data, the Mann-Whitney U test was used to determine whether the difference between the two groups was statistically significant. The Student's t-test was used for continuous variables that were normally distributed. For correlation, the Pearson correlation analysis was utilized. A value of $p<0.05$ was considered as statistically significant.

Results

In this study, 90 adolescents ≤18 years of age who were admitted with various reasons to the outpatient clinics were accepted into the study. The median age of all patients in the study was 11±4 years. The subjects were divided into two groups; the first group consisted of those patients who were assessed for vitamin D levels and the other laboratory measurements at the end of winter (n=46), the second group consisted of those patients who were assessed for the same laboratory features at the end of summer (n=44). The two groups were compared in terms of demographic, clinical and laboratory characteristics.

Table I shows the demographic characteristics and laboratory results of adolescents who were evaluated at the end of winter and summer. The mean age of the participants of the winter group was 12.5±2.6 years and of the summer group 11.3±2.1 years. When the two groups were compared in terms of age, there was a significant statistical difference ($p<0.05$).

Of the winter and summer groups, 45.7% and 45.5% were male, respectively. There was no significant difference in gender ($p>0.05$). The median vitamin D levels were as follows; for the end of the winter period; 28.1±16.9 nmol/L and for the end of the summer period; 25.4±19.2 nmol/L. This parameter is not statistically significant for the groups ($p=0.288$). The Vitamin D deficiency percentage of the study group for the end of the winter period was 60.8% and for the end of the summer period, it was 15.9% but this was not significantly statistically significant. The Vitamin D

Table I. The demographic characteristics and laboratory results of the adolescents

	End of Winter group (n=46)	End of Summer group n=44)	p value
Demographic data			
Age, years (mean ± SD)	12.5±2.6	11.3±2.1	0.016*
Gender Male, n (%) Female, n (%)	 21 (45.7) 25 (54.3)	 20 (45.5) 24 (55.5)	0.985†
Exposure to sunlight, minute (mean ± SD)	96.7±69.5	100.6±94	0.622*
Traditional clothing (mother), n (%) Yes No	 26 (56.5) 20 (43.5)	 20 (45.5) 24 (54.5)	0.399†
Acidic beverage consumption, n (%) Yes No	 29 (63.1) 17 (36.9)	 28 (63.6) 16 (36.3)	1.0‡
Sunscreen use, n (%) Yes No	 7 (15.3) 39 (84.7)	 7 (15.9) 37 (84.1)	0.928†
Daily physical activity (h/week) (mean ± SD)	1.7±1.3	2.5±2	0.082*
Laboratory Findings			
Ca (mg/dL), median, (IR)	9.8 (0.6)	9.9 (0.5)	0.119*
P (mg/dL), median, (IR)	4.6 (0.9)	4.9 (0.5)	0.149*
Mg (mg/dL), median, (IR)	2.1 (0.3)	2.1 (0.2)	0.461*
ALP (U/L), median, (IR)	200 (142)	199 (98)	0.386*
PTH (pg/mL), median, (IR)	42.4 (24.5)	43.2 (19.5)	0.283*
Vitamin D level (nmol/L), median, (IR)	28.1±16.9	25.4±19.2	0.288*
Vitamin D insufficiency, n (%)	41 (93.2)	18 (39.2)	0.082†
Vitamin D deficiency, n (%)	28 (60.8)	7 (15.9)	0.387†

*Mann-Whitney U test; †chi-square test; ‡Fisher's exact test; SD: Standard deviation, Ca: Calcium, IR: Interquartile range, P: Phosphorus, Mg: Magnesium, ALP: Alkaline phosphatase, PTH: Parathyroid hormone

insufficiency percentage of the summer group was higher than the winter group (93.2% vs. 39.2%, p>0.05). The frequency of vitamin D deficiency was significantly higher in girls (10.2%) than in boys at the end of the summer group (p=0.042, data not shown). However, the end of the winter group had no difference in terms of gender. There were also no differences between the groups in terms of laboratory findings including Ca, Mg and the other bone parameters.

The mean sun exposure time of the two groups was similar. Traditional clothing (covering the entire body except the face and hands) was very rare for both study groups (3.5% and 5.9%, data not shown). However, almost half of the subjects' mothers used the traditional clothing. The daily use of Ca was determined to be mostly low in both groups; for summer, it was 3.7% and 4.2% (not shown) for the winter group. When the groups were analyzed for acidic beverage consumption, its frequency was similarly high in both groups (63.6% for summer and 63.1% for winter). Sunscreen use was slightly higher in the summer group than in the winter one (15.9% vs. 15.3%). The mean daily physical activity of both groups was similar (for summer 1.7 hrs and for winter 2.5 hrs daily, p=0.082).

Discussion

In this study, we evaluated whether there is a significant difference of vitamin D status in terms of a seasonal pattern and whether there is an association between several other factors and vitamin D deficiency. The vitamin D in our populations of adolescents showed a high percentage (34.4%) in İzmir, Turkey. The relative prevalence of vitamin D deficiency, insufficiency and sufficiency varies in different studies according to the different cut-offs for specifying the optimal vitamin D status. It is reported that the prevalence of both vitamin D deficiency and insufficiency increased in 10-15 years from 22% to 41% between 1988 and 2004, with an increase in the prevalence of subclinical vitamin D deficiency from 53% to 71% in United States of America (USA) (11). A systematic review (168.000 participants) reported that 88.1% of the participants had mean 25-OHD values below 75 nmol/L, 37.3% had mean values below 50 nmol/L and 6.7% had mean values below 25 nmol/L (12). Cashman et al. (13) stated that 13.0% of the 55.844 European individuals had serum 25-OHD concentrations <30 nmol/L on average in the year, with 17.7% and 8.3% in those sampled during the extended winter (October-March) and summer (April-November) periods, respectively. Another study conducted by Karagüzel et al. (14) reported that the prevalence of vitamin D deficiency was 93% during spring and 71% during autumn in 746 healthy students aged between 11 and 18 years. They also declared that the age, sex and Ca level were found to be independent predictors for vitamin D deficiency and that vitamin D deficiency was higher in girls than boys (87%, 78%, respectively). In Beirut, a study reported that vitamin D deficiency was 65% in the winter season and 40% at the end of the summer (15). In our study, the vitamin D level of the winter group was 28.1 nmol/L and the summer group was 25.4 nmol/L and the winter group was 60.8%, there was no statistical significance in both groups. However, vitamin D insufficiency at the end of winter was prominently higher than the summer group. We could not find any relationship between the seasonal pattern and the other factors. Moreover, the girls who wore traditional dress covering the entire body had concentrations not lower than 15 nmol/L. In our population, although there was a high frequency of vitamin D deficiency, the PTH was within the normal range in both groups.

During the Industrial Revolution, vitamin D deficiency appeared in epidemic form in temperate zones where the pollution from factories blocked the sun's ultraviolet rays. Thus, vitamin D deficiency is probably the first childhood and adolescent disease caused by environmental pollution. In terms of the time of exposure to sunlight, as expected, the end of our summer group had higher levels than those at the end of our winter group, but this was not statistically significant. In winter time, due to the fact that there is inadequate sunlight, increased pollution and the factor of being 32° N, it leads to inadequate production of vitamin D in the skin, vitamin D levels are very low during winter (16).

The link between vitamin D deficiency and rickets is well understood. However, subclinical vitamin D deficiency may also be detrimental to bone health in childhood. Its effects on bone mineralization have the potential to result in lower peak bone mass being attained, which could in turn contribute to increased fracture risk in both childhood and older adult life. Unfortunately, natural foods containing vitamin D are limited. To protect bone health in children and adolescents and for public health policy, the aim should be to ensure sufficient vitamin D intakes in the majority of the world population (12). In Turkey, the Ministry of Health started free vitamin D supplementation for every infant to protect against deficiency and rickets. However, there is no national vitamin D fortification program in children and adolescents with a vitamin A deficiency who have a tendency to skeletal disorders. The Endocrine Society clinical practice guideline recommends that infants and children aged from 0-1 year require at least 400 IU/d (IU=25 ng) of vitamin D and children 1 year and older require at least 600 IU/d (17). Vitamin D deficiency is common in our rural and urban areas among adolescents so we believe that they need vitamin D supplementation regularly.

Increased PTH levels associated with low vitamin D levels have been known for a long time. A study reported that there is a negative correlation between 25-OHD and PTH. It has also been reported that an increase in PTH level occurs at 25-OHD levels between 25 and 82.5 ng/mL (7,34-37) and serum PTH levels start to rise as 25-OHD levels decline below

35.8 nmol/L (14). In our study, we could not find a correlation between PTH and vitamin D levels in the two groups via *Pearson correlation* analysis.

The determination of a winter-time subclinical vitamin D insufficiency of 39.2% is in agreement with the findings of another study from Turkey (18). Our healthy adolescent population findings show a problem even in the sunny climate of Turkey. The relationships between vitamin D and Ca intakes of adolescents indicates that an adequate daily Ca intake is important and provides protection to our adolescents from insufficiency. Akman et al. (19) evaluated 849 healthy children between 1-16 years and they found that the prevalence of vitamin D deficiency (<20 ng/mL) was 8% and that of vitamin D insufficiency was 25.5% in the population investigated. Also, they reported that the average daily intake of Ca was especially low in the >8-year-old age group (<1300 mg/day) similar to our study. In our current study, the daily Ca intake was low in 60.3% of all patients and 63.3% consumed acidic beverages. Similar to our study, Akman et al. (19) revealed that the intake of Ca was found to be low, especially in school children and adolescents. Previous studies conducted in two urban areas of Turkey reported that the daily Ca intake was found to be very low (266 mg/day) in adolescent girls (18).

There were no statistically significant differences in the laboratory results between the two groups. There were also no statistically significant correlations between serum vitamin D status and subjects' diet, periods of exposure to sunlight, the use of sunscreen, regular physical activities, traditional clothing of mothers or clothing style in our study.

There are several limitations of the present study. The major one is that the present study is focused on only 90 healthy adolescents, so the study sample population size was small. Another limitation is that the study was conducted in western Turkey; thus, our results are not necessarily true for the entire Turkish population and all geographical regions.

Our findings suggest that vitamin D deficiency and insufficiency is an important problem among apparently healthy Turkish adolescents especially at the end of the winter period and especially for females. We recommend supplemental vitamin D intake and outdoor activities for sunlight exposure to improve the vitamin D status of adolescents. We also suggest that vitamin D supplementation should be necessary for adolescents, and the guidelines should be modified for children and adolescents in terms of adequate vitamin D intake in Turkey.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Informed consent was obtained from the parents or guardians of all eligible children.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: G.G., Ş.G., A.A., Z.K., G.K., Design: Ş.G., Data Collection: G.G., Ş.G., A.A., Analysis or Interpretation: G.K., A.A., Z.K., Literature Search: Z.K., G.K., Writing: Ş.G.

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

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References

1. Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M; Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. Pediatrics 2008;122:398-417.
2. Hollis BW. Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. J Nutr 2005;135:317-22.
3. Callaghan AL, Moy RJ, Booth IW, Debelle G, Shaw NJ et al. Incidence of symptomatic vitamin D deficiency. Arch Dis Child 2006;91:606-7.
4. Gordon CM, DePeter KC, Feldman HA, Grace E, Emans SJ et al. Prevalence of vitamin D deficiency among healthy adolescents. Arch Pediatr Adolesc Med 2004;158:531-7.
5. Munns CF, Shaw N, Kiely M, et al. Global Consensus Recommendations on Prevention and Management of Nutritional Rickets. J Clin Endocrinol Metab 2016;101:394-415.
6. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011;96:1911-30.
7. Mansbach JM, Ginde AA, Camargo CA Jr et al. Serum 25-hydroxyvitamin D levels among US children aged 1 to 11 years: do children need more vitamin D? Pediatrics 2009;124:1404-10.
8. Saintonge S, Bang H, Gerber LM et al. Implications of a new definition of vitamin D deficiency in a multiracial us adolescent population: the National Health and Nutrition Examination Survey III. Pediatrics 2009;123:797-803.
9. Manios Y, Moschonis G, Hulshof T et al. Prevalence of vitamin D deficiency and insufficiency among schoolchildrenin Greece: the role of sex, degree of urbanisation and seasonality. Br J Nutr 2017;118:550-8.
10. Gonzalez-Gross M, Valtuena J, Breidenassel C, et al. Vitamin D status among adolescents in Europe: the Healthy Lifestyle in Europe by Nutrition in Adolescence study. Br J Nutr 2012;107:755-64.
11. Ginde AA, Liu MC, Camargo CA Jr. Demographic Differences and Trends of Vitamin D Insufficiency in the US Population, 1988-2004. Arch Intern Med 2009;169:626-32.
12. Hilger J, Friedel A, Herr R, et al. A systematic review of vitamin D status in populations worldwide. Br J Nutr 2014;111:23-45.
13. Cashman KD, Dowling KG, Skrabáková Z, et al. Vitamin D deficiency in Europe: pandemic? Am J Clin Nutr 2016;103:1033-44.
14. Karagüzel G, Dilber B, Çan G, Ökten A, Değer O, Holick MF. Seasonal Vitamin D Status of Healthy Schoolchildren and Predictors of Low Vitamin D Status. J Pediatr Gastroenterol Nutr 2014;58:654-60.

15. El-Hajj Fuleihan G, Nabulsi M, Choucair M, et al. Hypovitaminosis D in healthy schoolchildren. Pediatrics 2001;107:53.
16. Webb AR, Kline L, Holick MF. Influence of season and latitude on the cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. J Clin Endocrinol Metab 1988;67:373-8.
17. Holick MF, Binkley NC, Bischoff-Ferrari HA et al. Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2011;96:1911-30.
18. Olmez D, Bober E, Buyukgebiz A, Cimrin D. The frequency of vitamin D insufficiency in healthy female adolescents. Acta Pædiatrica 2006;95:1266-9.
19. Akman AO, Tumer L, Hasanoglu A, İlhan M, Çaycı B et al. Frequency of vitamin D insufficiency in healthy children between 1 and 16 years of age in Turkey. Pediatr Int 2011;53:968-73.

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Original Article

Neonatal Kidney Dimensions and Medullary Pyramid Thicknesses According to the Weight, Length and Body Mass Index of Newborns

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ABSTRACT

Aim: The primary purpose of the present study was to investigate the relationship between neonatal kidney dimensions and medullary pyramid thicknesses (MPTs) according to the weight, length and body mass index (BMI) of newborns.
Materials and Methods: A total of 237 [128 (54%) boys and 109 (46%) girls] consecutive term newborns in the first month of life were evaluated. Infants with an underlying renal disease, urinary symptoms, chromosomal abnormalities or low birth weight were excluded from the study. Greyscale ultrasound of neonatal kidneys was performed in standard transverse and longitudinal planes. Renal dimensions, parenchymal thickness and MPT were also evaluated and compared with neonatal age, height, weight, BMI and abdominal circumference (AC) and head circumferences (HC). Regression analyses were performed and graphs were plotted to determine the independent factors for renal parameters.
Results: Statistically significant associations were noted in the renal dimensional measurements among neonatal weight (NW), neonatal length, BMI, HC and AC in the infants ($p<0.0001$). However, no statistically significant difference was observed between right kidney MPT and NW, HC, AC and BMI. In contrast, a statistically significant association was detected between left kidney MPT and NW, HC, AC and BMI.
Conclusion: Neonatal kidney length, neonatal kidney width and renal parenchymal thickness measurements could be a useful method as an indicator of neonatal growth.
Keywords: Newborn, renal dimensions, parenchymal thickness, medullary pyramid thickness, neonatal weight

Introduction

The development of the kidney is associated with an increase in the number of nephrons. The kidneys of infants with low birth weight are smaller due to the small number of glomeruli and nephrons (1).

The number of nephrons and glomeruli was determined before birth using a biological variation (1). The development of nephrons has been observed to be completed at 32-34 weeks of gestation, and post-partum nephron development does not occur in babies (2,3). The number of nephrons varies from person to person, although it is believed that there are about a million nephrons per kidney in humans (4). Since the kidney parenchyma contains glomeruli and kidney filtration systems, the measurement of renal parenchymal thickness is believed to be a more sensitive indicator of kidney growth (5). Some diseases such as renal cystic diseases, vesicoureteral reflux and ureteropelvic junction obstruction and also genetic background affect renal parenchymal thickness. In previous studies, intrauterine parenchymal growth was evaluated by

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measuring renal parenchymal thickness (6). In addition, renal parenchymal thickness in low birth weight infants versus normal birth weight infants has been investigated (1).

A correct evaluation of kidney size is very important for clinical diagnosis and treatment. In several diseases, changes occur in the size and morphology of the kidneys. It is important to follow up the kidney dimensions of patients ultrasonographically (USG) in cases such as recurrent urinary tract infections, vesicoureteral reflux and neurogenic bladder. Acute kidney damage (AKD) is a common disorder and often has a severe outcome in neonatal intensive care units. The incidence of AKD in newborns is related to the gestational week, birth weight, postnatal weight and the facilities of the neonatal intensive care unit which affects the prognosis (7). Such diseases can affect renal morphology and size by causing parenchymal atrophy or hypertrophy. Kidney length is the quantitative measurement that is most often used for comparing results determined in accordance with the follow-up study of renal size standards (8-10). Therefore, renal evaluation of healthy newborns is very important to understand pathological changes.

Hence, US imaging has been regarded as the gold standard for the evaluation of renal morphology in newborns. A number of studies have been conducted to determine the normal range of kidney size using sonography. To the best of our knowledge, there has been no study with a large sample size investigating the morphology of kidneys, including "renal medullary pyramid length, kidney size and parenchymal thickness" in newborns. Measurements of the kidneys of children and adults have been established using US previously (8,11-14); however, there are limited available data on neonatal renal dimensions and the length of medullary pyramids.

The primary purpose of the present study was to investigate the relationship between neonatal kidney dimensions and medullary pyramid thicknesses (MPTs) according to the weight, length (NL) and body mass index (BMI) of newborns in a large series.

Materials and Methods

Study Population

The study patients were sampled from the patient population treated at the Department of Neonatology in the University of Health Sciences, Training and Research Hospital, Trabzon between January 2016 and September 2016. A total of 249 individuals were seen in our Radiology department, and renal US evaluation was performed for those full-term babies (i.e. having completed 37 weeks of gestation) without urinary tract symptoms or underlying renal problems. Infants with congenital chromosomal abnormalities, those born by caesarean section and those small for gestational age were excluded. A total of 12 infants were excluded from the study because of abnormalities incidentally detected by sonographic evaluation (7 hydronephrosis, 1 nephrocalcinosis and 4 surrenal haematoma). Finally, a total of 237 infants [128 (54.0%) boys and 109 (46.0%) girls] were evaluated.

The study was approved by the local Institutional Review Board, and all participants' parents provided written informed consent. This prospective, single-institution study was conducted in compliance with the Declaration of Helsinki and the good clinical practice guidelines of the Ministry of Health of Turkey. The study was approved by the Local Ethics Committee of Kanuni Training and Research Hospital, Trabzon, Turkey (approval number: 2016/10 date 09/03/2016).

All ultrasound examinations were performed within the first month after birth using an Aplio 500 ultrasound machine (Toshiba Medical Systems, Co., Ltd., Otawara, Japan) equipped with linear 4.8- to 11-MHz transducers. All the examinations were performed by a radiologist (H.A.A.K.) with more than 10 years of experience in neonatal imaging. The examinations were performed according to international recommendations and guidelines for the safe use of diagnostic ultrasound in medicine (15).

Ultrasound Imaging

After breastfeeding from the mother, the babies were made to relax and prepared for the US examination. A clean examination bed was prepared before each examination for the protection of babies against contamination. Probes containing baby skin solutions with no harmful effects were used for disinfection. For the comfort of the newborns, bottle warmers were used to maintain a constant body temperature to make the ultrasound procedures more comfortable.

We initially started with B-mode sonographic imaging using an Aplio 500 ultrasound machine (Toshiba Medical Systems, Co. Ltd, Otawara, Japan) equipped with linear 4- to 9-MHz transducers. The aim of using linear transducers was to detect more detail in the anatomic images. After selecting the linear transducers, we selected the neonatal abdomen mode and then selected wide screen trapezoid mode for visualizing the upper and inferior pole of the kidney at the same time with a best resolution. The depth was zoomed in to adjust for a perfect image of the medullary pyramids. If necessary, we increased the focus degree but not the number of foci that were placed at the level of kidney. Finally, we adjusted for a perfect view of the neonatal kidney.

The patient was placed in the contralateral decubitus position over a special pillow that was built for the comfort of the babies. Greyscale US evaluation of both kidneys was performed in standard transverse and longitudinal planes. The maximum vertical and transverse dimensions of each kidney were measured by the examiner (Figure 1).

Renal medullary pyramid length was also measured in the longitudinal plane. Echogenicity and incidental pathologies were evaluated.

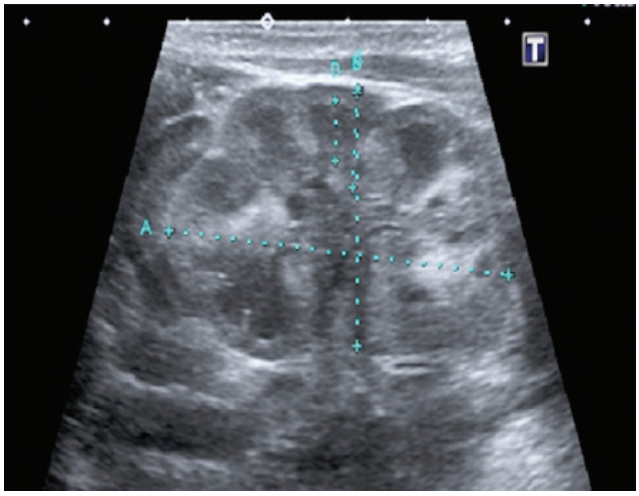

Figure 1. Gray scale evaluation method for neonatal kidney. The maximum vertical A) and transverse B) dimensions, parenchymal thickness C) of kidney was measured (D) of kidney was measured

Statistical Analysis

Statistical analysis was conducted using SPSS 22.0 statistical software.

Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed in percentages. Regression analyses were performed to determine the independent factors for renal parameters. Multiple linear regression analysis was performed to analyze the relationship between USG measurements and somatic measurements. Pearson's correlation test was used to evaluate the correlations of continuous variables, and p values <0.05 were considered as statistically significant.

Results

A total of 237 term newborns comprising 109 (46%) girls and 128 (54%) boys were evaluated in this study. Mean gestational age, weight and height of the term infants were 39.2±1.01 weeks, 3.534±519 g and 50.6±1.08 cm, respectively. The clinical and demographic characteristics of the patients are shown in Table I.

Mean head circumference (HC), abdominal circumference (AC) and BMI were 35.6±0.90 cm, 38.0±2.26 cm and 0.22±0.02, respectively.

A significant association was observed between right kidney length (RKL) and neonatal weight (NW) (r=0.259, p<0.0001). Furthermore, the relationship between right kidney width (RKW)-NW (r=0.382, p<0.0001) and right kidney parenchymal thickness-NW (r=0.241, p<0.0001) was also statistically significant.

Other neonatal clinical variables such as NL, HC, BMI and AC also showed a statistically significant association between both kidney diameters apart from the right kidney MPT.

Table I. The clinical and demographic characteristics of patients

Variables	Mean ± SD
Age (week)	39.2±1.01
NW (g)	3534±519
NL (cm)	50.6±1.08
HC (cm)	35.6±0.90
BMI (cm)	0.22±0.02
AC (cm)	38.0±2.26
RKL (cm)	45.01±4.83
RKW (cm)	21.20±3.20
RKPT (cm)	9.1±1.10
RKMPT (cm)	5.60±3.20
LKL (cm)	45.17±5.82
LKW (cm)	21.34±2.86
LKPT (cm)	9.27±1.06
LKMPT (cm)	5.86±1.07

SD: Standard deviation, NW: Neonatal weight, NL: Neonatal length, HC: Head circumference, BMI: Body mass index, AC: Abdominal circumference, RKL: Right kidney length, RKW: Right kidney width, RKPT: Right kidney parenchymal thickness, RKMPT: Right kidney medullary pyramidal thickness, LKL: Left kidney length, LKW: Left kidney width, LKPT: Left kidney parenchymal thickness, LKMPT: Left kidney medullary pyramidal thickness

The regression analysis graphs depicting the relationships between left kidney length (LKL)-NL and RKW-NW are shown in Figure 2,3.

The correlation results between renal parameters and clinical variables are shown in Table II. Regarding the independent factors for renal parameters, the regression analyses revealed that NW (95% CI: 0.000-0.004, p=0.029) and HC (95% CI: 0.120-1.704, p=0.024) were independent markers of RKL. In addition, NL (95% CI: 0.780-2.546, p<0.0001) was found to be an independent marker of LKL.

Discussion

The present study has shown that renal dimensions, parenchymal thickness and left kidney MPT are related to the BMI and weight of the infant. The size of the kidneys and the medullary parenchymal thickness showed no association with age in the first 30 days of life.

The renal parenchyma consists of the renal cortex and the medullary pyramids. These structures may also be evaluated using computed tomography or magnetic resonance imaging (MRI), as well as by ultrasound (12,13). MRI, which is an expensive imaging modality, is particularly difficult to administer in children because of the requirement of sedation. Conversely, US is a non-invasive, cost-effective and easily accessible imaging modality that can be used for the rapid evaluation of neonatal kidneys. US also does not involve ionizing radiation (11).

In newborns, physical examination methods such as palpation and percussion are inadequate to evaluate kidney size. Radiography, intravenous pyelography and radionuclide studies are not preferred in routine practice for the evaluation of neonatal kidneys due to radiation risks and difficulties in application. In addition, renal diameters assessed by conventional radiological investigations other than US may be about 16% larger than their actual size. Several factors may be responsible for this oversizing, such as the centration of the tube and the change in distance from the patient (photographic magnetization) or because of respiration, the osmotic effect of the contrast agent (chemical magnetization) or various other reasons such as renal axis variations.

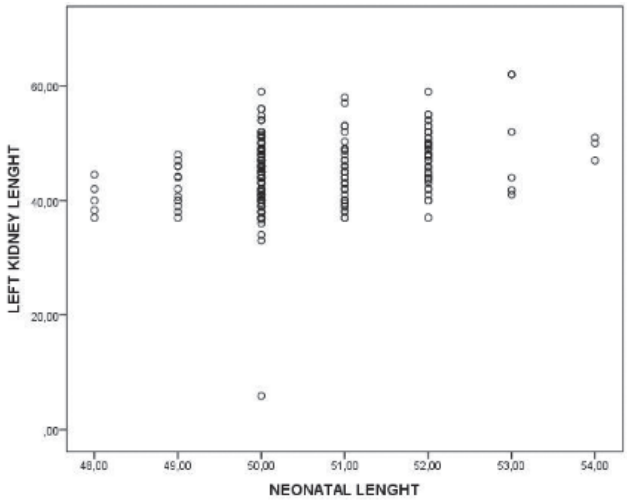

Figure 2. Regression graph for left kidney length and neon natal length

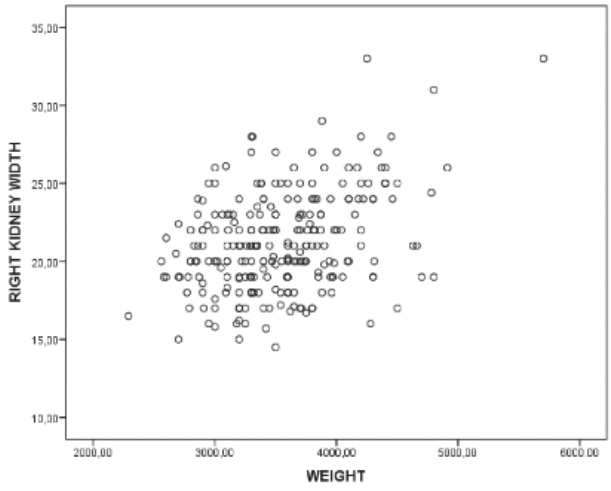

Figure 3. Regression graph for right kidney width and neonatal weight

A previous study reported that weight indicated the best correlation with neonatal kidney measurements in the first week of life (16). However, only 1-week newborns were included and renal parenchymal thickness and MPT were not evaluated in that study. Furthermore, although HC, AC and BMI are important measurements for the evaluation of infant development in newborn intensive care units, that study did not include these parameters.

Some studies have reported that renal parenchymal thickness might be used as a measure of renal growth in low birth weight infants versus normal birth weight infants (1). However, the smallest functional unit of the kidney is the renal glomerulus and the renal glomerulus present in the cortex. The renal parenchymal thickness is the sum of the thicknesses of the cortex and the medullary pyramids. Therefore, MPT must also be assessed to calculate the functional unit, i.e. the cortex.

There is little information regarding the relationship between MPT and BMI. Eze et al. (17) found a weak correlation between MPT and BMI and a moderate positive correlation between MPT and weight. However, we did not find any association between MPT and BMI in our study. There may be several explanations for this discrepancy. First, the study populations are different. Eze et al. (17) included patients aged up to 18 years, and neonatal populations accounted for a very small proportion of that population. In contrast, our study

Table II. Correlation between renal parameters and clinical variables

Variables	NW (g)	NL (cm)	HC (cm)	BMI (cm)	AC (cm)
RKL (cm)	r=0.259	r=0.226	r=0.305	r=0.260	r=0.273
RKW (cm)	r=0.382	r=0.325	r=0.247	r=0.251	r=0.342
RKPT (cm)	r=0.241	r=0.152	r=0.125	r=0.194	r=0.141
RKMPT (cm)	r=0.037	r=0.019	r=0.029	r=0.020	r=0.030
LKL (cm)	r=0.244	r=0.340	r=0.203	r=0.155	r=0.224
LKW (cm)	r=0.381	r=0.274	r=0.216	r=0.325	r=0.368
LKPT (cm)	r=0.313	r=0.189	r=0.209	r=0.319	r=0.266
LKMPT (cm)	r=0.238	r=0.161	r=0.163	r=0.252	r=0.198

NW: Neonatal weight, NL: Neonatal length, HC: Head circumference, BMI: Body mass index, AC: Abdominal circumference, RKL: Right kidney length, RKW: Right kidney width, RKPT: Right kidney parenchymal thickness, RKMPT: Right kidney medullary pyramidal thickness, LKL: Left kidney length, LKW: Left kidney width, LKPT: Left kidney parenchymal thickness, LKMPT: Left kidney medullary pyramidal thickness

population is exclusively neonatal and the population size is relatively larger than their study population. Second, genetic factors might have a potential impact on the evolution of MPT.

Conclusion

In conclusion, we have demonstrated that renal dimensional measurements and parenchymal thickness can also be used as a marker for evaluating postnatal growth of a newborn.

Renal dimensional measurements and parenchymal thickness could be a useful method as an indicator of neonatal growth. In newborns, kidney measurements are independent from postnatal age but related with the development of the baby. Therefore, renal nomograms need to be determined according to the somatic parameters of neonates.

Declaration of Interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Kanuni Training and Research Hospital Local Ethics Committee (approval number: 2016/10 date 09/03/2016).

Informed Consent: All participants' parents provided written informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.A.A.K., Design: H.A.A.K., Ş.K., Data Collection or Processing: H.A.A.K., Ş.K., Analysis or Interpretation: H.A.A.K., Writing: H.A.A.K.

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

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References

1. Brennan S, Kandasamy Y. Renal parenchymal thickness as a measure of renal growth in low-birth-weight infants versus normal-birth-weight infants. Ultrasound Med Biol 2013;39:2315-20.
2. Bagby SP. Developmental origins of renal disease: should nephron protection begin at birth? Clin J Am Soc Nephrol 2009;4:10-3.
3. Askenazi DJ, Ambalavanan N, Goldstein SL. Acute kidney injury in critically ill newborns: what do we know? What do we need to learn? Pediatr Nephrol 2009;24:265-74.
4. Hoy WE, Douglas-Denton RN, Hughson MD, Cass A, Johnson K, Bertram JF. A stereological study of glomerular number and volume: preliminary findings in a multiracial study of kidneys at autopsy. Kidney Int Suppl 2003:31-7.
5. Hricak H, Slovis T, Callen C, Callen P, Romanski R. Neonatal kidneys: sonographic anatomic correlation. Radiology 1983;147:699-702.
6. Hadar E, Davidovits M, Mashiach R, et al. Sonographic evaluation of kidney parenchymal growth in the fetus. Arch Gynecol Obstet 2012;286:867-72.
7. Timovska SN, Cekovska S, Tosheska-Trajkovska K. Acute kidney injury in newborns. Pril (Makedon Akad Nauk Umet Odd Med Nauki) 2015;36:83-9.
8. Rosenbaum D, Korngold E, Teele RL. Sonographic assessment of renal length in normal children. AJR Am J Roentgenol 1984;142:467-9.
9. Klare B, Geiselhardt B, Wesch H, Schärer K, Immich H, Willich E. Radiological kidney size in childhood. Pediatr Radiol 1980;9:153-60.
10. Han BK, Babcock DS. Sonographic measurements and appearance of normal kidneys in children. AJR Am J Roentgenol 1985;145:611-6.
11. Christophe C, Cantraine F, Bogaert C, et al. Ultrasound: a method for kidney size monitoring in children. Eur J Pediatr 1986;145:532-8.
12. Dinkel E, Ertel M, Dittrich M, Peters H, Berres M, Schulte-Wissermann H. Kidney size in childhood sonographical growth charts for kidney length and volume. Pediatr Radiol 1985;15:38-43.
13. Konuş OL, Ozdemir A, Akkaya A, Erbaş G, Celik H, Işik S. Normal liver, spleen, and kidney dimensions in neonates, infants, and children: evaluation with sonography. AJR Am J Roentgenol 1998;171:1693-8.
14. Zerin JM, Blane CE. Sonographic assessment of renal length in children: a reappraisal. Pediatr Radiol 1994;24:101-6.
15. Barnett SB, Ter Haar GR, Ziskin MC, Rott H-D, Duck FA, Maeda K. International recommendations and guidelines for the safe use of diagnostic ultrasound in medicine. Ultrasound Med Biol 2000;26:355-66.
16. Soyupak SK, Narli N, Yapicioğlu H, Satar M, Aksungur EH. Sonographic measurements of the liver, spleen and kidney dimensions in the healthy term and preterm newborns. Eur J Radiol 2002;43:73-8.
17. Eze CU, Akpan VP, Nwadike UI. Sonographic assessment of normal renal parenchymal and medullary pyramid thicknesses among children in Enugu, Southeast, Nigeria . Radiography 2016;22:25-31.

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Original Article

Evaluation of Oral and Dental Health Status in Hemophilic Children and Adolescents in the City of Rasht

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ABSTRACT

Aim: Patients with hemophilia need special care and attention in dentistry. Thus, we assessed the oral and dental health status in children and adolescents with hemophilia in Rasht, Iran.

Materials and Methods: In this case-control study, 53 hemophiliac patients (A and B), 2-15 years of age, and 53 healthy children were assessed. A checklist including demographic data was filled out and the subjects were examined by one dentist. The patients were assessed for modified gingival index, plaque index (PI) and Decayed-missing-filled teeth [(DMFT) in permanent teeth and Decayed-missing-filled teeth (dmft) in primary teeth)] indices. Data were analyzed with SPSS 19 at a significance level of $p<0.05$.

Results: The mean age of the subjects was 10.49±4.21 years in the case group and 10.5±4.07 years in the control group. 92.5% of the patients exhibited factor VIII deficiency and the most frequent blood group was A (34%). 63.2% of the subjects in the hemophilia group and 13.2% in the control group had a history of bleeding that was significant (p=0.0001). There were significant differences between the two groups in bleeding at tooth eruption and exfoliation sites of deciduous teeth (p=0.0001), flossing (p=0.046), toothpick use (p=0.02) and the history of dental education (p=0.014). No significant difference was found between dmft and DMFT scores between the two groups but DMFS was significantly higher in the hemophilia group (p=0.007). There was also a significantly higher PI in the hemophilia group (p=0.003).

Conclusion: Considering some unsatisfactory oral health conditions in these patients, dental health care and prevention seems necessary and can be effective in the prevention of dental problems, bleedings and complex treatments.

Keywords: Hemophilia, MGI index, DMFT index

Introduction

Treatment of patients with hereditary hemorrhagic conditions is associated with many problems. One of these conditions is hemophilia, which is the most common recessive x-linked hereditary hemorrhagic condition, with these affected patients comprising a sizeable proportion of patients with special conditions (1). This disease afflicts males at a ratio of 1:10.000 of the world population in all the ethnic groups (2). The prevalence of the disease is 1:9.800 of the population in Iran (3).

Hemorrhage from different areas of the oral cavity and gingival bleeding might be profuse and continue for a long time. Even the physiologic processes of tooth eruption and exfoliation might be associated with long periods of hemorrhage. Hemophilia pseudo-tumor in the mandible is a condition that might occur due to frequent sub-periosteal hemorrhage (4). Other oral manifestations, including a high

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rate of caries and widespread periodontal diseases, mostly appear to be secondary due to neglecting the oral cavity due to other systemic conditions and bleeding of oral tissues due to tooth-brushing. Oral ulcers are the common reason for hemorrhage in children with severe forms of hemophilia (2,5). Intracranial hemorrhage, might leave serious sequelae and is one of the main etiologic factors for death in such children (6).

Patients with hemophilia require special attention and care during different dental procedures. Given the expenditure devoted to such patients annually, it is very important to follow different aspects of the health of such patients. Therefore, the present study was undertaken to evaluate the oral and dental health of children and adolescents with hemophilia in Rasht, Iran.

Materials and Methods

In the present descriptive-analytical study, all the 53 children and adolescents with hemophilia in Rasht, Iran, who were 2-15 years of age, were evaluated. In addition, a control group (n=53) with no hemophilia, was selected from schoolchildren in Rasht, who were matched in relation to socio-economic status based on their parents' jobs and educational status, and age and gender with the hemophilia group.

A questionnaire was prepared by the dentist for both groups, which consisted of questions about their parents' educational level and job, history of bleeding in the oral cavity, the frequency of tooth-brushing, oral hygiene habits, history of routine dental visits, dental therapeutic needs and the history of regular fluoride therapy. The type of hemophilia, the factor level, the laboratory tests [human immunodeficiency virus (HIV), hepatitis C virus (HCV) antibody and hepatitis B virus surface (HBs) antigen] and the blood type of the hemophilia group were also extracted from the medical records of the patients.

Clinical evaluations for all the subjects were carried out by one operator while the patients were sitting on a chair based on the guidelines of the World Health Organization (7). Modified gingival index (MGI) and plaque index (PI) were used for the evaluation of periodontal status and Decayed-missing-filled teeth [(DMFT) in permanent teeth and Decayed-missing-filled teeth (dmft) in primary teeth] indices were used for the evaluation of dental caries in both groups.

DMFT and dmft indices were evaluated with the use of a blunt explorer and a flat dental mirror with the tactile and visual technique (4).

MGI (described by Loe and Silness) was used to evaluate gingival inflammation. To this end, examinations were carried out with the use of a flat mirror and observation of the gingiva with no dental probe. In this context, a five-score classification was used as follows:

Score 0 = no inflammation,

Score 1 = mild inflammation: minor changes in the color and consistency of the gingiva in all the gingival portions but not at all the gingival margins and interdental papillae,

Score 2 = mild inflammation: similar to score 1 but with the involvement of all the margins and papillae,

Score 3 = moderate inflammation: shining, rubor and edema or hypertrophy of the gingival margins or interdental papillae,

Score 4 = severe inflammation: clearly visible rubor, edema and hypertrophy of the marginal gingiva and interdental papillae in association with spontaneous bleeding, congestion and/or ulceration (4).

O'Leary PI was used to determine PI with the use of fuchsin plaque disclosing agent. After the patient has rinsed, the dentist examines the four surfaces of each tooth (except the occlusal surface) for accumulation of stain at the dento-gingival junction. After all teeth are examined and scored, the index is calculated by dividing the number of plaque containing surfaces by the total number of available surfaces. (8).

Statistical Analysis

Data were analyzed with SPSS 19 at a significance level of $p<0.05$ with chi-squared test, Kolmogorov-Simonov test, Mann-Whitney U test, Fisher's exact test and Kruskal-Wallis test.

Ethical Approval

All procedures performed in studies involving human participants were approved by the Ethics Committee of Dental School, Guilan University of Medical Sciences and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Therefore, all the parents of the participants gave informed consent for inclusion in this study.

Results

The subjects consisted of 52 boys (98.1%) and one girl (1.9%) in each group. All the 53 patients with hemophilia were negative for HIV, HCV antibody and HBs antigen (which was not possible for the control group subjects).

Figure 1 presents the frequencies of bleeding in the oral cavity in both the control and hemophilia groups. Chi-squared test revealed that the history of bleeding in the whole oral cavity ($p=0.0001$), tooth eruption site ($p=0.0001$) and tooth exfoliation site ($p=0.0001$) were significantly higher in the hemophilia groups.

Figure 2 presents the frequencies of oral and dental hygiene habits in the two groups. Chi-squared test revealed that the use of dental floss and toothpicks in the children and adolescents with hemophilia was significantly less frequent than that in the control group ($p=0.046$, $p=0.02$).

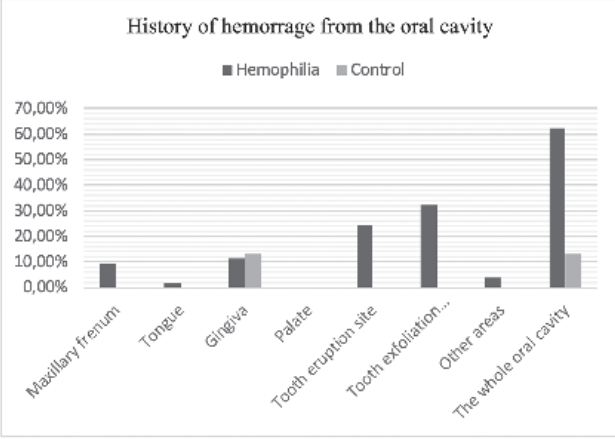

Figure 1. The frequencies of bleeding from the oral cavity in the control and hemophilia groups

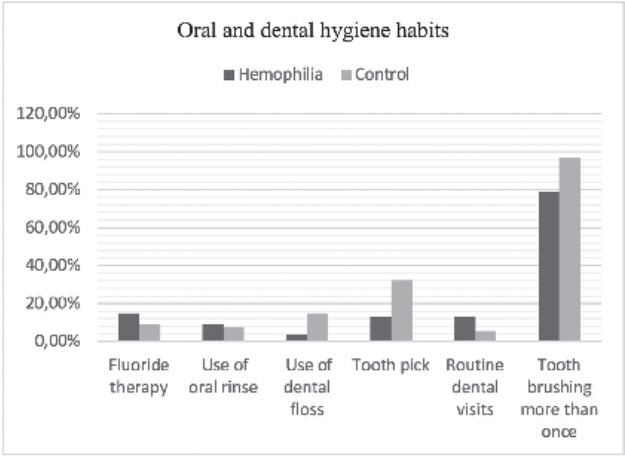

Figure 2. The frequencies of oral and dental hygiene habits in the two study groups

In addition, the frequency distributions of dental anomalies (p=0.67), fluorosis (p=0.49), hypoplasia (p=1.0) and treatment needs (p=0.49) were evaluated in the two groups and no significant differences were detected between them. 96.2% of the subjects in the control group and 100% of the patients with hemophilia required dental treatment. The most required services in the hemophilia group were caries-stopping care (83%) and prevention (79.2%) and in the control group were prevention (92.5%) and caries-stopping care (83%) respectively.

Table I compares the means of dmft, DMFT, Decayed Missing Filled Surface in permanent teeth (dmfs), Decayed Missing Filled Surface in permanent teeth (DMFS), PI and MGI between the two groups. Kolmogorov-Simonov test showed that none of the data of the parameters above were distributed normally in the two groups. Mann-Whitney U test revealed that the means of DMFS and O'Leary index were significantly higher in the hemophilia group (p=0.007 and p=0.003).

Comparison of the means of MGI, PI, DMFT and dmft separately for each hematologic factor in those children and adolescents with hemophilia is presented in Table II. Kolmogorov-Smirnov test showed that data in relation to DMFT and dmft and PI and MGI were not distributed normally in subjects with hemophilia (p<0.05). In addition, Kruskal-Wallis test showed that only the difference in MGI was significant in terms of the hematologic factors (p=0.011).

Table III presents the frequency distributions of deficiencies of different factors and factor levels in children and adolescents with hemophilia in the present study. The greatest deficiency was related to factor VIII (92.5%), followed by factor IX (5.7%) and factor VII (1.8%). Also, the most frequent factor level of deficiency was <1% (52.8%), followed by 1-5% (26.4%) and >5% (20.8%).

Discussion

The oral manifestations in patients with hemophilia appear in different forms. Hemorrhage from different parts of the oral cavity and from the gingiva might be profuse and continue for a long time. Even the physiologic processes of tooth eruption and exfoliation might be associated with long-term hemorrhage.

In the present study, the highest rate of hemorrhage in patients with hemophilia were related to the exfoliation of deciduous teeth and tooth eruption, followed by bleeding from the gingiva, maxillary frenum and tongue, in descending order.

Those subjects with hemophilia used brushes and dental floss at a significantly lower frequency compared to the control group, which might be due to fears of bleeding in the oral cavity; however, there were no significant differences between the two groups in relation to the use of mouthwashes, fluoride therapy and dental visits.

In addition, the dmfs index was not significantly different between the two groups, which might be attributed to the high prevalence rate of interproximal caries in deciduous teeth. However, the DMFS index in those children and

Table I. The characteristics of the two study groups

	Hemophilia Mean ± SD	Control Mean ± SD	p value
DMFT	2.75±2.71	1.98±2.51	0.112
DMFS	3.79±4.1	2.03±4.05	0.007
dmft	2.83±3.06	3.13±3.21	0.66
dmfs	4.9±6.2	6.58±7.33	0.25
The O'Leary index	81.87±15.43	72.78±18.94	0.003
MGI	1.86±0.8	1.75±1.1	0.3

SD: Standard deviation, DMFT: Decayed-missing-filled teeth, MGI: Modified gingival index

adolescents with hemophilia was significantly higher than that in the control group (3.79 vs. 2.3), indicating the presence of multi-surface caries in subjects with hemophilia, which might be attributed to the lower rate of use of dental floss and toothpicks.

A higher DMFS index in patients with hemophilia compared to the control group might be attributed to coagulation problems in patients with hemophilia; therefore, these patients prefer soft foods and liquids to decrease the risks of ulceration of the oral cavity mucosa. However, it should be considered that the mucosa in these subjects is not fragile and is only prone to bleeding; therefore, the best diet suggested for these patients is low-volume soft food with a high content of calorie and a low content of carbohydrates (2).

In a study by Salem and Eshghi (9), DMFT, DMFS, dmft and dmfs did not exhibit significant differences; however, there were more restored teeth in subjects with hemophilia compared to the control subjects. The differences between results of above mentioned study with ours, may probably attributed to lack of specialized dental care centers for Hemophilia patients in the city of Rash. As a result, they seek care into major Hemophilia dental clinics in other centers. Such centers and advanced facilities with free services for patients with hemorrhagic problems are available in Tehran to solve the health problems that these patients have in relation to their oral cavities.

In the present study, 92.5% of the patients with hemophilia had factor VIII deficiency and the rest had deficiencies of factors VII and IX. The factor levels were <1% in 32.8% of the subjects (severe) and 1-5% in 26.7% of the subjects (moderate). However, in a study by Noor et al. (10), 75 subjects (87%) had hemophilia A (47% with mild form and 30% with severe form) and the rest had hemophilia B (55% with mild form and 36% with severe form), indicating a higher prevalence of the severe form in Rasht in this age group.

In addition, in the present study, 96.2% of the subjects in the control group and 100% of the subjects with hemophilia required dental treatment, indicating poor oral hygiene in all groups in the society. Lack of attention to oral hygiene during childhood might result in dental and oral complications and morphological changes during adulthood, indicating the importance of paying more attention to dental care in all children. The best healthcare services in all the age groups, in both healthy children and children with special diseases, including hemophilia, should include attention to the prevention of dental diseases. Therefore, in addition to a decrease in the complications of oro-dental diseases in all age groups, the economic costs, time and morbidity in relation to diseases decrease significantly.

The PI in the patients in the hemophilia group might be explained by the way such patients brush their teeth and their avoidance of toothbrush contact with the gingiva and possible hemorrhage after brushing.

These patients comprise a small proportion of the population; however, they exert high treatment costs on the health systems (9).

Comprehensive hemophilic care consists of all the

Table III. Frequency distributions of deficiencies of different factors and factor levels in children and adolescents with hemophilia

Factor	No.	Percentage	Factor level	No.	Percentage
Factor VIII	49	92.5	<1%	28	52.8
Factor IX	3	5.7	1–5%	14	26.4
Factor VII	1	1.8	>5%	11	20.8
Total	53	100	Total	53	100

Table II. Comparison of the means of Decayed-missing-filled teeth, dmft, plaque index and Modified gingival index separately for the level of each hematologic factor in the children and adolescents with hemophilia

	Factor level	No.	Mean	SD	p value
DMFT	<1%	28	2.35	2.45	p=0.173
	1-5%	14	2.28	2.46	
	>5%	11	4.36	2.26	
dmft	<1%	28	2.75	2.8	p=0.122
	1-5%	14	4.21	3.8	
	>5%	11	1.27	1.79	
O'Leary index	<1%	28	80.43	19.6	p=0.818
	1-5%	14	83.61	7.43	
	>5%	11	83.32	10.4	
MGI	<1%	28	1.96	0.83	p=0.011
	1-5%	14	2.14	0.66	
	>5%	11	1.27	0.64	

SD: Standard deviation, DMFT: Decayed-missing-filled teeth, MGI: Modified gingival index

medical services, including dental services. Prevention of dental problems is the main principle in oral care and might result in the avoidance of emergency events. Some of these procedures consist of brushing of the teeth with a fluoridated toothpaste, use of a soft or medium toothbrush, use of fluoride supplements, limiting the use of carbohydrates, use of non-cariogenic sugars and dental visits at least once a month for check-up, fluoride therapy and sealant therapy if necessary. At the same time, the health of periodontal tissues to prevent hemorrhage and tooth loss is of the utmost importance.

Recommendations

It is suggested that training sessions be held by the authorities for dentists in order to support the health of patients with special conditions, especially hemophilia. It is helpful to establish a special center for the oral health problems of hemophiliacs in Rasht in order to solve their problems in this respect. Also, ignoring these patients and lack of treatment for such patients by dentists all over Gilan Province due to problems in relation to long and un-controllable bleeding and avoiding such responsibility, due to fears about HIV and HBV etc. necessitate the establishment of a center to support these patients in Gilan Province.

Ethics

Ethics Committee Approval: The study was approved by Ethics Committee of Dental School, Guilan University of Medical Sciences (approval number: IR.GUMS.REC.1394.407).

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

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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

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References

1. Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. Coagulation Disorders, Harrison's principles of internal medicine, 19th ed. New York, McGraw Hill Education, 2015.
2. Sanders BJ, Shapiro AD, Hock RA, Weddell JA, Belcher CE. Management of the medically compromised patient. McDonald and Avery Dentistry for the Child and Adolescen. 9th ed. St. Louis, Mo, Elsevier Inc, 2011. p. 408-509.
3. Eshghi P, Mahdavi-Mazdeh M, Karimi M, Aghighi M. Haemophilia in the developing countries: The Iranian experience. Arch Med Sci 2010;6:83-9.
4. Makarem M, Talebi M, Mazhari F, Kiyanosh N. Evaluation of Oral and Dental Health Status of Khorasan Province Hemophilic Patients in 2004. J Mashhad Dent School 2008;32:161-8.
5. Fonseca MA. Oral and dental care of local and systemic diseases. Pediatric Dentistry-Infancy through Adolescence. 4th ed. St. Louis, Mo. Elsevier Saunders, 2005. p. 74-6.
6. Kliegman RM, Behrman RE, Jenson HB, Stanton BM. Nelson textbook of pediatrics. 20th ed. Philadelphia, Pennsylvania, Elsevier Inc, 2016. p. 2384-9.
7. Alpkiliç Baskirt E, Ak G, Zulfikar B. Oral and general health-related quality of life among young patients with haemophilia. Haemophilia 2009;15:193-8.
8. Newman MG, Takei H, Klokkevold PR, Carranza FA. Carranza's Clinical Periodontology: Expert Consult. 12th ed. St. Louis, MO. Elsevier Inc, 2014.
9. Salem K, Eshghi P. Dental health and oral health-related quality of life in children with congenital bleeding disorders. Haemophilia 2013;19:65-70.
10. Noor N, Maxood A, Mumtaz R. Dental management of haemophilic pediatric patients. Pak Oral Dent J. 2012;32.1.

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Original Article

A Qualitative Study Exploring the Needs of Turkish Mothers in the Pediatric Intensive Care Unit

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ABSTRACT

Aim: Mothers have different needs, depending on their cultural and religious backgrounds, and these need to be known and acknowledged by the pediatric intensive care unit (PICU) professional staff. To date, limited studies have been conducted in Turkey, a majority Muslim country, which analyzes the needs of mothers whose children are in PICU. The purpose of this study was to explore parents' needs in a child hospital's PICU in Turkey.
Materials and Methods: A descriptive exploratory qualitative study. Individual, semi-structured interviews of a purposive sample of 9 mothers were carried out between December 2013 and May 2014. The mothers who were enrolled to participate in the interviews were with an average age of 27.4 years in PICU of a major children's hospital in Turkey.
Results: In the content analysis, the main themes of "being sure of receiving the best care, having needs fulfilled, being able to cope with emotional feelings" were created.
Conclusion: This study presents the disruptions during the PICU process, the fact that it is a difficult process for the mothers and they have many needs during this process and these needs have to be fulfilled.
Keywords: PICU, qualitative, Turkish mother, nursing

Introduction

Being a parent of an infant or a child who has been placed in intensive care is a very difficult experience. Scholars always seek a way to reduce this difficult experience for the families. Included among the causes of stress for families with a child in intensive care are the severity of the disease of the child, the need for mechanical ventilation, the appearance of the child during this period, the concerns of the family regarding the child's future, the appearance of the intensive care unit and its attendant sounds and interventions, the changes in the roles family members must assume and the feelings of uncertainty and despair. In this situation called a family event, most of the parents face psychological negativities (1-6). Within the last 20 years, in addition to the studies performed that examine the said sources of stress on the families, various studies, involving multidisciplinary teams and a variety of research methods, have been conducted in different cultures and geographic locations that have sought to determine the most important needs of the families in order to obtain universal and predictable data (7). During the critical period, in which the child is in a state of hemodynamic imbalance, the nurses may be under the belief that the needs of the family are matters that should be handled at a later time. However, by determining and fulfilling the needs of the family in the early period, at the time the child is admitted to the intensive care unit, the negative effects of stress can be reduced (7). Meeting needs of parents in accordance with the

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principles of the family-centered approach not only provides a trust-based relationship between parents and nurses but also increases parental satisfaction (1,8,9).

According to Ames et al. (10), the needs reported to be most important were "being by the child during his/her care and being involved in the care, having trust in the health professionals and being informed of the course of the child's health condition and treatment", while Al-Mutair et al. (11) found that "disclosure of information, trust, spiritual care, ongoing connection with the patient and involvement in and support for the care" were key. Moreover, in another study, the parents' need of trust was found to be much more important than the need for physical resources or support (12). However, Berube et al. (13) emphasized the need for comfort in the pediatric intensive care unit (PICU) in their study and stated that families were interested in having the security of physical, emotional and psycho-social comfort. Intensive care nurses are health professionals who are in the best possible position to provide support for patients and their families. Nurses provide a sincere and individual care that allows them to develop trust-based relationships with patients and their families, to assess their needs, and to monitor reactions given to changing conditions of the patient by the family members (14). The perception of needs and expectations of the families differ according to ethnical and cultural backgrounds (15,16). According to a systematic compilation by Shudy et al. (17) that reviewed six studies, parents were shown to have needs ranging from being able to communicate with their children, having an understanding about the changes in their condition, having a feeling of hope and being assured that their children are getting the best treatment to being able to maintain the caregiver role, strengthening the family relationship and being provided with accurate information. In the developing country of Turkey, where most of the population is Muslim, one study was conducted that focused on this topic. In this study by Sülü and Başbakkal (18), the spiritual needs of the mother were determined, and other needs, in addition to moral support, such as good care, understanding and provision of information on the health of the child, were cited as being important.

Materials and Methods

Aim

This study aimed to conduct an in depth, detailed examination of the needs of mothers whose children were admitted to the PICU.

Study Design and Setting

To examine these needs, a qualitative research method, using a phenomenological design, was chosen for this study. The purposeful sampling method used to determine the participants resulted in the selection of mothers of nine children who were in the PICU. It was determined that only a small sample group be used, as qualitative studies require that a detailed analysis be made of each case. Inclusion criteria used for participation in the study required that the mother be the primary care provider of a child who had been hospitalized in the PICU for more than 3 days between December 2013 and May 2014 and that the mother agreed to participate in the study, was able to speak and understand Turkish and was older than 18 years of age. The study was conducted in a large district hospital with an intensive care unit containing 24 beds. The 368-bed-capacity hospital has been providing healthcare services in İzmir since 1957. The PICU is composed of three sections. In the first section, which houses children who are in an overall stable condition of health, the children are able to stay with their caregivers. Mothers are involved in their child's care and training and preparation for home care are also performed. All types of intensive care patients, except those with sepsis, are accepted. In the second and third sections, however, constant parent companionship is not permitted. In these sections, according to hospital regulations, parents are only allowed to visit their children two days a week.

Data Collection

As part of the qualitative research method, the semi-structured interview method was used for data collection. The interview form was prepared by examining the relevant literature on the experiences of the families whose children were treated in the PICU (Table I). The interview consisted of five open-ended questions, with the addition of a set of alternative questions available at the end of the interview form. The interviews were conducted on a date and at a time most suitable for the mothers participating in the study, and a private room within the PICU was used to ensure that the interview was carried out in a comfortable manner. Two mothers not involved in the study were interviewed to test the intelligibility of the interview questions and the ease of being able to answer them. The responses of these two mothers were neither recorded nor included in the study. The questions found to be difficult to understand and thereby hard to answer by these two mothers were rephrased before finalizing the interview form. A voice recorder was used, after

Table I. Interview form

1. What do you think about the appearance of the PICU?
-What do you think about the physical features of the PICU?
2. What are your thoughts on the attitude of the health personnel?
3. What are your needs here, from the time your child was first admitted to the PICU to now?
-What are your physical, emotional and social needs here?
4. How do you feel about the fact that your child is in the PICU?
5. How do you cope with these feelings and thoughts you are experiencing?

PICU: Pediatric intensive care unit

obtaining prior consent from the mothers, to record the interviews, each of which lasted between 20-50 minutes.

Data Analysis

The interview data were evaluated using content analysis. To secure the validity and reliability of the research, each interview was transcribed, without the addition of comments. Internal and external reliability was accomplished through strict compliance with the strategies of LeCompte and Goet (19). The transcribed interviews were transferred to a Microsoft Office document and compared with the voice recordings of the interview. Codes were created from interviews that were separately transcribed by two different researchers. The codes created by the researchers were gathered together, out of which the themes formed would serve as the outlines of the study findings (Table II).

Internal homogeneity and external heterogeneity were taken into account as the themes were being created. Particular attention was given to ensuring that the themes were different from each other, the categories and codes of the themes had internal integrity and the themes had integrity with each other. The study sample was determined according to the number of participants it took before reaching data saturation. In other words, as the themes started to repeat and no new codes and themes occurred, the data collection process was finalized.

Ethical Consideration

Prior to the start of the study, approval to conduct the study was obtained from the İzmir Health Science University Dr. Behçet Uz Child Hospital (approval number: 1339918). Before starting the interview, participants were provided with an explanation of the purpose of the study and were informed that participation was voluntary and that they were free to end the interview at any time. Written and verbal consent was obtained from the mothers who agreed to participate in the study.

Table II. Main themes and sub-themes of the study

Themes	Sub-themes	Codes
Certainty of receiving the best care	Perception	A place where good care is provided to the children and they are attended to, kept in stable condition and undergo recovery, and where treatments are administered, families cannot enter, and the setting is clean / Hygienic
	Hygiene deficiency	Common areas of use / Air conditioning / Baby food preparation conditions / Materials / Insufficient barriers at the entrance of PICU
	High risk of infection / Possibility of transmission	Postponement of discharge due to nosocomial infection / Risk of recurrence of disease Number of patients in the intensive care unit / High number of medical procedures
	Attitude of the health personnel	Good / Helpful / Supportive / Protective / Talkative / Friendly / Caring Bad / Insecure / Reproving / Not caring / Unequal behavior / Difference in behaviors / Not smiling / Grumpy / Not Likeable / No empathy
	Lack of care	Not giving a bath to the child / Not moisturizing the child's body Having the care provided by the companions
Fulfillment of needs	Being beside the child	Not being able to see the child / Not being able to be together with the child when she cries
	Need for information	Not being able to participate in the visits / Curiosity
	Need for comfort	Eating / Sleep / Improper conditions of bath and restroom / improvement / Bath and restroom in separate places / Not being able to change clothes
	Family's routine	Care of other children / Not being able to spare time for the other members of the family / Quitting job / Argument with the spouse-separation
Coping with attendant emotions	Feeling	Trying to feel good / Trying to think that the child will get better / To hope Uncertainty / Torment / Being tired out / Blaming herself / himself / Despair / Waiting for the child to die / Being afraid of the death of the child / Pain / Being very miserable / Anxiety / Sorrow / Anger
	Religious belief	Pray / Reading the Quran / Taking sanctuary in God / Reciting prayers / Being patient
	To distract	Consoling himself/herself / Trying to stay strong / Showing himself / Herself strong / Smiling at life / Cheering oneself up / Seeing a psychologist Dreaming / Spending time on the phone / Walking around / Going to the supermarket
	Support	Spouse / Relative / Friend Insufficiency of the people who will support / Difficulty of coming from another city / Problem of finding a place to stay

PICU: Pediatric intensive care unit

Results

The average age of the mothers was 27.4 and their educational backgrounds varied between primary school and university graduates. The period of hospitalization of the children in the PICU varied between 5 days and 9 months. For the children, who had been admitted to the PICU as a result of severe medical diagnoses, their age varied between 3 months and 7 years, and 5 of them were males and 4 of them were females (Table III).

According to the content analysis, three main themes were developed: "Certainty of receiving the best care", "fulfillment of needs" and "coping with the attendant emotions" (Table III).

1. Certainty of Receiving the Best Care

Perception

The mothers perceive the PICU as a clean, hygienic place which is clean/hygienic, where good care is provided to the children, children are attended to at all times, children undergo recovery, children are kept in stable health, treatments are administered and families cannot enter. The mothers responded to this question as follows: "Health personnel standing by my child in order to attend to them immediately" [4 Mothers (M)]; "I thought it would be a place we wouldn't be able to enter...a very hygienic place" (7 M); "provide the best care...they are always there to help" (8 M).

Hygiene Deficiency

Despite believing that the PICU would be clean and hygienic, the mothers did not find the physical environment to actually be hygienic. Most of the mothers mentioned the physical shortcomings of the PICU, describing it as a "dirty place, with beds close to dirty sinks and poor air-conditioning." Others stated, "this place doesn't look like a PICU" and "people should be required to wear overshoes and gloves, but they are not" (9 M).

Risk of Infection

All of the mothers mentioned the risk of their children acquiring an infection, and most of them stated that their children did indeed get an infection and that their discharge was postponed due to the high number of patients. In particular, they noted, "the first thing I think about is the infection..." (1 M); "my child acquired an infection in the PICU" (2 M); "afraid that she will acquire an infection..." and "I want to get out of this hospital as soon as possible" (8 M).

Attitude of the Health Personnel

The positive and negative statements from the mothers regarding the health personnel included, "they help us...", "they are very warm and friendly and they tend to us..." and "I can talk to the nurses and they always support and take good care of us" (1 M); "I do not look at the monitor screen, so they would comfort us by telling us to not be afraid because nothing was going to happen" (8 M); "...the nurse scolded me..., some of them treated me in a nice manner but others were bad" (5 M); "some were grumpy..., I cannot trust the nurses..., one of them just recently yelled at a mother very badly" (7 M); "she is also a mother like me and therefore would also be hurt if something happened to her child" (8 M).

Lack of Care

Regarding this issue, the mothers expressed, "our child cannot have a bath..., they have only one wash basin and tub and all of the sick children are washed there" (1 M); "I have been here for 1.5 months and I would not let my child be washed, even if they wanted to because the place is very dirty" (7 M); "there is definitely nothing here in terms of care" (9 M).

Table III. Characteristics of the participants

Participant No.	Age	Educational Background	Period/days of hospitalization in the PICU	Age of the child	Diagnosis of the child
1	25	Primary school	50	2 years	Biotinidase deficiency, epilepsy, pulmonary infection
2	23	Middle school	90	11 months	Spinal Muscular Atrophy
3	23	High school	120	1 years	Epilepsy
4	38	University	620	1 years	Spinal Muscular Atrophy
5	28	Primary school	270	7 years	Cerebral Palsy
6	24	Middle school	7	5 months	Ventricular Septal Defect, Atrial Septal Defect, Patent Ductus Arteriosus
7	25	High school	46	3.5 months	Epilepsy
8	32	High school	5	3 months	Cardiomegaly
9	29	Primary school	5	7 years	Bronchial Asthma

PICU: Pediatric intensive care unit

2. Fulfillment of Needs

Being Beside the Child

Almost all of the mothers stated that their most basic need was "being beside the child". One of the mothers said "I was so afraid when they told me that I could not stay with my child, but now I am close to my child" (2 M). Another said "I could not see my daughter or have access to her as she cried, but now I am beside her" (5 M).

Need for Comfort

The mothers felt that PICU was extremely uncomfortable and expressed problems involving food, sleeping, bathing, restroom and changing clothes. The mothers explained their discomfort about this matter as follows; "I had to eat next to my child. I wish there was a separate room and no smell of food...", (4 M); "it would be nice if the restroom and sink were separate...", "it is disgusting...", "you cannot take a bath or change your clothes" (5 M); "I am not happy with the place I am sleeping", "both of my sides are hurting, but I will put up with everything for the sake of my child" (6 M).

Need for Information

One of the most important needs of the mothers is the provision of information. The mothers expressed their concerns on this matter as follows: "When they perform visits, they remove us from the room, do not directly tell you that she could die or that we could lose her" (8 M); "information should be provided right after the visit, but no information was provided" (9 M).

Family's Routine

The mothers stated, in the following expressions, that their family routines were disrupted: "I have another son and he needs me a lot, but I cannot take care of him." (1 M); "my husband quit his job and came here, like me"..., "we suffered disappointment, and now our family life has been disrupted" (4 M); "my husband and I argue from time to time"..., "until this time, I had not been separated from my husband like this" (6 M).

3. Coping with Attendant Emotions

Feelings

One of the mothers expressed her feelings regarding having her child in the PICU as follows: "I tell myself that my child is going to be fine" (6 M); "most of the mothers have negative feelings...", "uncertainty, this makes me very sad" (3 M); "I blame myself. I did not take care of him well. If I had, he would not be sick. I am guilty" (9 M); "despair...waiting for my child to die" (2 M); "my world has crashed down around me...I am still sad and worried..." (8 M).

Religious Belief

These responses constitute themes of religious belief, support and distraction. "God is my helper. I pray and read the Qur'an" (4 M); "I pray to God and recite prayers; try to be patient" (7 M).

To Distract

Here are some statements from mothers who coped with their negative emotions using methods outside of religious beliefs: "This psychologically affects me a lot. I try to stand, ...I have people who need me and therefore, I want to be strong" (1 M); "by smiling, I try to keep living my life, talking about my problems, it makes me feel good, it cheers me up, s/he says don't be sad, s/he is going to live with the help of God, s/he supported me a lot, I can cope due to all this support" (6 M); "if you tell your loved ones, they will be sad...my sleep helps me. I see my child standing and smiling, it will be fine, I see things like this and it makes me feel better" (4 M).

Support

Most of the mothers expressed that they receive support from their spouses, relatives and friends in the following manner: "I can share it with my husband, my closest relatives, I do not like sharing it with the other moms because their psychology is not good" (1 M); "there were our friends whom we met here, their child was discharged, so we talk on the phone" (3 M); the mothers stay as companions of all patients in the PICU. The mothers also talked about the difficulty of the situation, saying the following: "I do not have any relatives here, so I cannot leave my child and go. I am always here" (4 M); "my husband cannot stay as there is no place for him to sleep here, and it is very far away, so he comes in the mornings and goes back in the evenings" (7 M).

Discussion

The findings obtained from the study were discussed within the context of three main themes:

Certainty of Receiving the Best Care

In the intensive care unit where the study was conducted, as the children and the mothers share the room, the mothers were able to closely witness all of the behavior, positive and negative, directed towards their children. Therefore, the mothers' perception of the intensive care environment was largely affected by this situation. In a study by Latour et al. (20), parents whose child was alone in the room describe the environment as peaceful, quiet and private. Diaz-Caneja et al. (21), in their study, described parents as "tubes surrounding their children" and focused on physical features. They mentioned that while many of the healthcare professionals made the parents feel secure, the appearance of the children was a matter of concern worrying for the parents.

In our study, the mothers voiced positive and negative thoughts on the attitudes of the healthcare personnel. In

order to replace negative perceptions with positive ones, the PICU nurses should develop greater awareness of this matter and review their approach to the families. The data from the study by Hall (22) showed that some families stated that the nurses were "kind, helpful, informative, and capable", while others complained that they were "the sole agency of care, ignorant, distressed and worried-looking". Our study, on the other hand, found that some of mothers expressed the positive aspects of the healthcare personnel, such as their supportiveness, willingness to talk and consideration. In the PICU (24-bed capacity) where the study was conducted, ten nurses work the day-shift and nine nurses work the night-shift. The patient/nurse ratio is approximately 2:4, and the tense, tiring working environment contributes to the nurses' failure to adopt a more patient oriented approach, keeping them stuck in a job oriented style of working. This situation explains why they sometimes have difficulties using efficient communication techniques when talking with mothers.

Another matter brought up by the families in our study was the lack of care. This is a particularly key point, as quality of care is one of the most important issues for families (23). Latour et al. (20) discussed family care coordination, suggesting that participation in the child's care is an important matter; however, this request should depend on the family - whether or not they feel ready - and the burden of care should not be completely on the family. Mattsson et al. (24) defined the meaning of care in the PICU as "building a sheltered atmosphere, meeting the child's needs and adapting the environment to family life". When a child is admitted to the PICU, the life of the family changes and they may feel like they have lost a part of their responsibilities (5). As they are accustomed to fulfilling all of the needs of their children at home, a disconnection between roles may occur as a result of the fulfillment of these needs being taken on by the healthcare personnel in the PICU (25).

Fulfillment of Needs

A majority of the mothers stated that their most basic need was "being beside the child". In the study by McKiernan and McCarthy (26), it was found that the primary source of stress for family members was not being able to see their children. In the PICU of our study, the mothers were allowed to be close to their children, and they were taken out of the room only in the event something unexpected occurred and during doctor or nurse visits. It is essential that the doctors and nurses talk to the families at the end of the visit and inform them of the child's prognosis. Almost all studies mention that the patient's relatives need sufficient and accurate information (11,13,23).

The mothers stated that the PICU was extremely uncomfortable and cited problems relating to food, sleeping, bathing, the restrooms and changing clothes. The basic needs in the PICU, in terms of the familial need hierarchy, are physiological needs, such as sleeping and eating. The possibility of families getting involved in their child's care, providing social support, and most difficult of all, fulfilling their emotional needs, is greatly diminished when the physiological needs are not first fulfilled (13). Majdalani et al. (23) and Berube et al. (13) stated that, as families were in search of comfort, the PICU should be organized in such a way as to provide comfort to and meet the physical needs of the families.

Another matter that has a negative impact on family life during the PICU process is the disruption of the family's routine. Lam et al. (27) noted the impact of "rescheduling of family routine" on the involvement of the families in the child's care, while Mattsson et al. (24) mentioned the importance of "adapting the environment for family life". In our study, as stated before, the mothers of the children stayed with them. Therefore, most of them had to quit their jobs and ask their relatives to take care of their other children. The job-centered style of working that nurses practice results in neglect shown to the parents. The nurses responsible for caring for the children in the PICU should be facilitators in ensuring that all of the family members involved in the care of the child are in a position to provide social support to the mothers, in creating resting periods and in enabling them to have some time for themselves.

Being Able to Cope with Feelings

If the healthcare professionals are aware of the feelings experienced by the families, they will be better able to deal with them. Latour et al. (20) highlighted the idea of "intensity" and stated that the families have negative feelings about the PICU. The study by Hall (22) revealed that the PICU reminds people of death. Among the ways for dealing with their emotions, the most commonly expressed tool was religious belief. This result was not surprising in Turkey, as the country is predominantly Muslim. Majdalani et al. (23) cited "Dependence on God" and Al-Mutair et al. (11) "Faith in God, reading of the Qur'an, prayer and charity" as coping mechanisms in their studies. Many of the mothers stated that they received support from their husbands, relatives and friends. Berube et al. (13) and McKiernan and McCarthy (26) noted that the families needed support for dealing with the situation. The Islam-inspired fatalistic approach served as another coping mechanism. It is a common belief to take the negative situations for granted, as they are done at the discretion of God. With this understanding, God shall redeem his people from their sins in return for all the hardships they experienced; therefore, when rough times come upon them, then it is surely because God loves them.

Ethics

Ethics Committee Approval: The study was approved by the İzmir Health Science University Dr. Behçet Uz Child Hospital (approval number: 1339918).

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

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: D.B., G.Ö.G., Design: D.B., G.Ö.G., G.K.M., Data Collection or Processing: D.B., Analysis or Interpretation: D.B., G.Ö.G., Literature Search: D.B., G.Ö.G., G.K.M., Writing: D.B., G.Ö.G.

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References

1. Vasli P, Dehghan-Nayeri N, Borim-Nezhad L, Vedadhir A. Dominance of paternalism on family-centered care in the Pediatric Intensive Care Unit (PICU): An ethnographic study. Issues Compr Pediatr Nurs 2015;38:118-35.
2. Colville G, Darkins J, Hesketh J, Bennett V, Alcock J, Noyes J. The impact on parents of a child's admission to intensive care: integration of qualitative findings from a cross-sectional study. Intensive Crit Care Nurs 2009;25:72-9.
3. Needle JS, O'Riordan M, Smith PG. Parental anxiety and medical comprehension within 24 hrs of a child's admission to the pediatric intensive care unit. Pediatr Crit Care Med 2009;10:668-74.
4. Jee RA, Shepherd JR, Boyles CE, Marsh MJ, Thomas PW, Ross OC. Evaluation and comparison of parental needs, stressors, and coping strategies in a pediatric intensive care unit. Pediatr Crit Care Med 2012;13:166-72.
5. Mcdonald ME, Liben S, Carnevale FA, Cohen SR. An Office or a bedroom? Challenges for family-centered care in the pediatric intensive care unit. J Child Health Care 2012;16:237-49.
6. Delva D, Vanoost S, Bijttebier P, Lauwers P, Wilmer A. Needs and feelings of anxiety of relatives of patients hospitalized in intensive care units: implications for social work. Soc Work Health Care 2002;35:21-40.
7. Meert KL, Briller SH, Schim SM, Thurston CS. Exploring parents' environmental needs at the time of a child's death in the Pediatric intensive care unit. Pediatr Crit Care MeD 2008;9:623-8.
8. Ladak LA, Premji SS, Amanullah MM, Haque A, Ajani K, Siddiqui FJ. Family centered rounds in Pakistani pediatric intensive care settings: non-randomized pre- and post-study design. Int J Nurs Stud 2013;50:717-26.
9. Butler A, Copnell B, Willets G. Family-centred care in the paediatric intensive care unit: an integrative review of the literature. J Clin Nurs 2014;23:2086-100.
10. Ames KE, Rennick JE, Baillargeon S. A qualitative interpretive study exploring parents' perception of the parental role in the paediatric intensive care unit. Intens Crit Care Nurs 2011;27:143-50.
11. Al-Mutair AS, Plummer V, Clerehan R, O'Brien A. Needs and experiences of intensive care patients' families: a Saudi qualitative study. Nurs Crit Care 2014;19:135-44.
12. Meert KL, Schim S, Briller S. Parental bereavement needs in the pediatric intensive care unit: review of available measures. J Palliative Med 2011;14:951-64.
13. Berube KM, Fothergill-Bourbonnais F, Thomas M, Moreau D. Parents' Experience of the Transition with their Child from a Pediatric Intensive Care Unit (PICU) to the Hospital Ward: Searching for Comfort Across Transitions. J Pediatr Nurs 2014;29:586-95.
14. Adams JA, Anderson RA, Docherty SL, Tulsky JA, Steinhauser KE, Bailey DE Jr. Nursing Strategies to Support Family Members of ICU Patients at High Risk of Dying. Heart Lung 2014;43:406-15.
15. Hall EO. Being in an alien world: Danish parents' lived experiences when a newborn or small child is critically ill. Scand J Caring Sciences 2005;19:179-85.
16. Tseng Y, Verklan T. Fathers in situational crisis: a comparison of Asian and Western cultures. Nurs Health Sci 2008;10:229-40.
17. Shudy M, de Almeida ML, Ly S, et al. Impact of pediatric illness and injury on families: a systematic literature review. Pediatrics 2006;118(Suppl 3):203-18.
18. Sülü E, Başbakkal Z. Yoğun bakımda yatan çocuk hastaların annelerinin manevi bakım (Spiritüel Bakım) gereksinimleri (Spiritual care requirements of the mothers of the hospitalized children in intensive care units). J Turk Soc Intens Care 2013;11:17-24.
19. LeCompte MD, Goet JP. Problems of reliability and validity in etnographic research. Rev Educ Res 1982;52:31-60.
20. Latour JM, van Goudoever JB, Schuurman BE, et al. A qualitative study exploring the experiences of parents of children admitted to seven Dutch pediatric intensive care units. Intens Care Med 2011;37:319-25.
21. Diaz-Caneja A, Gledhill J, Weaver T, Nadel S, Garralda E. A child's admission to hospital: a qualitative study examining the experiences of parents. Intensive Care Med 2005;31:1248-54.
22. Hall EO. Danish parents' experiences when their new born or critically ill small child is transferred to the PICU-a qualitative study. Nurs Crit Care 2005;10:90-7.
23. Majdalani MN, Doumit MA, Rahi AC et al. The lived experience of parents of children admitted to the pediatric intensive care unit in Lebanon. Int J Nurs Stud 2014;51:217-25.
24. Mattsson JY, Arman M, Castren M, Forsner M. Meaning of caring in pediatric intensive care unit from the perspective of parents: A qualitative study. J Child Health Care 2014;18:336-45.
25. Graham RJ, Pemstein DM, Curley MA. Experiencing the pediatric intensive care unit: Perspective from parents of children with severe antecedent disabilities. Crit Care Med 2009;37:2064-70.
26. McKiernan M, McCarthy G. Family members' lived experience in the intensive care unit: a phemenological study. Intens Crit Care Nurs 2010;26:254-61.
27. Lam LW, Chang AM, Morrissey J. Parents' experiences of participation in the care of hospitalised children: a qualitative study. Int J Nurs Stud 2006;43:535-45.

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Original Article

The Results of Simulation Training in Pediatric Nursing Students' Education

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ABSTRACT

Aim: Simulation training that started with low realistic models in health education has developed in recent years and is now widely used in medicine and nursing education. The purpose of the present research is to compare nursing students' knowledge, skills, stress and anxiety during pediatric practices and to determine the students' satisfaction and confidence levels related to the use of simulation.

Materials and Methods: This randomized controlled study was conducted with 57 "third-year" students. The students were assigned to experimental (n=23) and control (n=34) groups. To collect the study data, a Student Information Form, Student's Satisfaction and Self-Confidence in Learning scale, Simulation Design scale, Educational Practices Questionnaire, Clinical Stress Questionnaire, State-Trait Anxiety Inventory, Nursing Care Knowledge Assessment Form for Children Suffering a Respiratory disease and Nursing Care Skill Assessment Form for Children Suffering a Respiratory disease were used. While the students in the experimental group had simulation training about Nursing Care of Child Suffering a Respiratory disease, the students in the control group were trained with traditional education methods. The students in both groups were observed while they gave care in the hospital environment.

Results: Clinical stress, state-trait anxiety and clinical skill scores of the students in the experimental group were higher than the control group. Simulation training contributed to the development of their self-confidence positively.

Conclusion: In this study, the simulation training was beneficial, and students' clinical application skill achievements improved.

Keywords: Pediatrics, nursing education, simulation

Introduction

Simulation training is an effective method of training which enables nursing students to gain skills in a controlled environment. Students who gain basic skills in a controlled environment perform healthcare interventions needed for the sick child and his/her family in the clinical setting more safely. Students are more successful in establishing a connection between theory and practice thanks to simulation training. Students are expected to perform interventions correctly without harming the child. Students are also expected to become prepared for clinical practice and to be more successful in performing interventions in pediatric patients through simulation training in an environment quite similar to actual practice environments in which patient reactions are revealed (1,2).

Respiratory-tract diseases are the most common diseases and the leading cause of deaths especially in children under the age of five worldwide (3,4). These diseases are also the leading cause of presentations to pediatric outpatient clinics, admissions to pediatric clinics, and antibiotic use especially in winter months, (5). According to the World Health Organization 2015 data, 16% of deaths in children under 5 years old occurred due to pneumonia. This rate

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is higher than the rates of deaths caused by diseases like human immunodeficiency virus, malaria or measles (6,7). A retrospective study conducted to investigate the causes of deaths in children aged 3 to 8 years in a hospital in the past 26 years reported that the rate of bronchopneumonia in diseases leading to deaths in children was 47% (8).

Since the provision of appropriate care and intervention in respiratory diseases that cause morbidity and mortality in millions of children all over the world is of importance, simulation training given in order to contribute to the development of psychomotor skills of working nurses and to support students with limited clinical experience in order to improve their clinical skills through nursing care scenarios regarding a child having a respiratory disease will make it possible to give appropriate care to a child with a respiratory disease (9-13). Therefore, this study was aimed at investigating the effect of simulation training on the knowledge, skills, stress and anxiety of third-year students taking a pediatric nursing course in clinical practice and to determine these students' satisfaction and self-confidence levels related to the use of simulation.

Materials and Methods

Type of Study: The study was conducted as a randomized control experimental study.

Hypotheses:

1. Clinical stress levels of students who receive simulation training are lower than those of students trained by traditional methods.

2. Anxiety levels of students who receive simulation training are lower than those of students trained by traditional methods.

3. The scores obtained from the Nursing Care Knowledge Assessment Form for Children Suffering a Respiratory disease by students who receive simulation training are higher than the scores obtained by those trained by traditional methods.

4. The scores obtained from the Nursing Care Skills Assessment Form for Children Suffering a Respiratory disease by students who receive simulation training are higher than the scores obtained by those trained by traditional methods.

5. Satisfaction and self-confidence levels of students who receive simulation training are higher than those of students trained by traditional methods.

Study Sample

The study was conducted with 57 third-year students taking the Pediatric Nursing course in the spring semester of 2016-2017 academic year. The Pediatric Nursing course includes 5 hours of theory and 8 hours of practice per week. All the students receiving the theoretical training were numbered on a list. Of them, 57 selected by a lottery method were randomly assigned to the experimental (n=23) and control (n=34) groups. While the students in the experimental group had simulation training, the students in the control group were trained with a traditional method. Students who have graduated from any of the health departments in high school education and/or are currently working in the field of health were excluded from the research.

Sample Size Calculation

In the Gpower statistical program, it was determined that 27 students should be sampled for each group according to the comparison of mean clinical stress score at a power of 0.80 and an acceptable Type I error size of 0.05 in groups.

Scenario

A 5-month-old infant with bronchopneumonia with nasal obstruction, coughing and wheezing complaints.

Students gain skills;

- Being able to evaluate the baby's physical examination results correctly,
- Being able to monitor the baby,
- Being able to apply nasal lavage to baby,
- Being able to give medication by nebulization,
- Being able to give oxygen to the baby,
- Being able to make attempts to calm the mother and the baby.

Data Collection Tools

Student Information Form: The Form includes 4 items questioning the students' age, gender, school achievement and rating of the simulation training.

Student Satisfaction and Self-Confidence in Learning scale: The 13-item original scale developed by Jeffries and Rizzolo (14) (2006) was adapted into Turkish by Unver et al. (15) (2017). The Turkish version of the scale has 12 items. The 5-point Likert-Type scale consists of 2 subscales: Satisfaction with Current Learning and Self-Confidence in Learning. The Cronbach's alpha value was 0.85 for the "Satisfaction with Current Learning" subscale, 0.77 for the "Self Confidence in Learning" subscale and 0.89 for the overall scale. The higher the total score obtained from the scale is, the higher the Student's Satisfaction and Self-Confidence is. In order to use the scale in the present study, permission was obtained from Unver et al. (15).

Simulation Design scale: This scale was developed by Jeffries and Rizzolo (14) (2006). The reliability and validity study of the Turkish version of the scale was conducted by Unver et al. (15) (2017). The Simulation Design scale has the following 5 subscales including 20 items: Objectives and Information, Support, Problem Solving, Feedback/Guided Reflection and Fidelity (Realism). The Cronbach's alpha values for the subscales were 0.77, 0.73, 0.76, 0.75 and 0.86 respectively. The Cronbach's alpha value for the overall scale was 0.90. The items in the scale are rated in two sections. In the first section, whether the best simulation design elements are implemented in simulation is rated. In

the second section, how important the simulation design elements are to the students is rated. High scores indicate that students' awareness of simulation design elements has increased. In order to use the scale in the present study, permission was obtained from Unver et al. (15).

Educational Practices Questionnaire: The scale was developed by Jeffries and Rizzolo (14) (2006). The reliability and validity study of the Turkish version of the scale was conducted by Unver et al. (15) (2017). The Educational Practices Questionnaire has the following 4 subscales including 16 items: Active Learning, Collaboration, Diverse Ways of Learning and High Expectations. The Cronbach's alpha values for the subscales and for the overall scale were 0.86, 0.61, 0.86, 0.85 and 0.91 respectively. The items in the scale are rated in two sections. In the first section, whether the best educational practice elements are implemented in simulation training is rated. In the second section, how important the educational practice elements are to the students is rated. In order to use the scale in the present study, permission was obtained from Unver et al. (15).

Clinical Stress Questionnaire: The scale developed by Pagana in 1989 to identify and assess the appraisal of stress in the first clinical experience of nursing students as threatening or challenging is a self-report Likert-Type instrument. The reliability and validity study of the Turkish version of the questionnaire was conducted by Sendir and Acaroglu (16) (2008). The questionnaire has 4 subscales: threat, fight, damage and benefit emotions. Each item is rated on a 5-point scale. While a low score indicates that the stress level is low, a high score indicates that the stress level is high. In order to use the questionnaire in the present study, permission was obtained from Sendir and Acaroglu (16).

State-Trait Anxiety Inventory (Self-Report Form) (STAI Form Tx ½): The State-Trait Anxiety Inventory developed by Spielberger et al. (17), and adapted to Turkish by Öner and Le Compte (18) (1985) includes 40 items. Of the items, 20 assess state anxiety and the other 20 assess trait anxiety. This inventory is administered to individuals over 14 years of age. In general, high levels of state and trait anxiety scores indicate a high level of anxiety, and individuals with scores above 60 need professional help.

Nursing Care Knowledge Assessment Form for Children Suffering a Respiratory disease: This form prepared in line with the literature and expert opinion was aimed at determining to what extent the students knew the health care to be given to a 5-month-old infant who was diagnosed with bronchopneumonia and had respiratory complaints such as nasal obstruction, coughing and wheezing. The form included 12 statements measuring the students' knowledge on the "Evaluation of Respiratory System in Children", "Oxygen Administration", "Medication Administration with Nebulizer" and "Intranasal Medication Administration". The students were asked to choose one of the 3 choices for each statement: "True", "False" or "I do not know".

Nursing Care Skill Assessment Form for Children Suffering a Respiratory disease: This form was aimed at determining how well the students implemented their skills of health care to be given to a 5-month-old infant who was diagnosed with bronchopneumonia and had respiratory complaints such as nasal obstruction, coughing and wheezing. Whether or not the students fulfilled the implementation steps included in the nursing skills regulations regarding "Evaluation of Respiratory System in Children", "Oxygen Administration", "Medication Administration with Nebulizer" and "Intranasal Medication Administration" was observed and assessed. The implementation steps were assessed by the researcher as "Fulfilled" or "Not Fulfilled". Expert opinion was obtained for the validity and reliability of the form.

Procedure

Before the study was conducted, approvals were obtained from the Non-Interventional Clinical Research Ethics Committee of İzmir Katip Çelebi University (approval number: 156/2017). Students were informed about the study and written consent was obtained from the volunteer students and then randomization was carried out.

Step 1: After the students were randomly assigned to the experimental and control groups, the Nursing Care Knowledge Assessment Form for Children Suffering a Respiratory disease was administered to all the students in the pre-simulation training period. It was a single-blind experiment. All the students were asked to use pseudonyms on the answer sheets for the pre-test and post-test.

Step 2: The students in the experimental group had the nursing care simulation training for children with a respiratory disease in two separate stations. During the simulation training, the students were observed in line with the Nursing Care Knowledge Assessment Form for Children Suffering a Respiratory disease. After the debriefing, the students were administered the Student Satisfaction and Self-Confidence scale in Learning, Simulation Design scale and Educational Practices Questionnaire.

Step 3: All the students were administered the Nursing Care Knowledge Assessment Form for Children Suffering a Respiratory disease after the training.

Step 4: All the students in both groups were administered the Trait Anxiety Inventory and PAGANA Clinical Stress Questionnaire.

Step 5: All the students in both groups were observed in line with the Nursing Care Skill Assessment Form for Children Suffering a Respiratory disease while they provided healthcare for a child with a respiratory disease during their 15-day clinical practices. Before the provision of healthcare was started, the students were administered the State Anxiety Inventory.

The simulation training was carried out in the fully equipped Nursing Skill Laboratory in two stations on two moderately realistic baby mannequins. The implementation of the scenario took about 15-20 minutes. In the scenario, the researchers involved in the study acted as nurses and mothers in both stations. Two researchers observed and evaluated the students. While the students gave care to an actual patient in a clinical setting, at least one researcher observed and evaluated them. To ensure compliance between observers, the researchers were trained on nursing care of the infant.

Statistical Analysis

In the research, descriptive statistics such as numbers, percentages and mean values were used. While the pre-and post-simulation training knowledge and skill scores of the experimental group were compared with the dependent Samples t-test (Wilcoxon). Knowledge, stress and anxiety scores of the experimental group were compared with those of the control group using the independent t-test (Mann Whitney U test). The experimental group's post-simulation training scores for the Student Satisfaction and Self-Confidence in Learning scale, Simulation Design scale and Educational Practices Questionnaire were assessed with the descriptive statistics. The statistical significance was accepted as $p<0.05$.

Results

The mean age of the students who participated in the study was 21.24±1.43 years. Of the students, 80.7% (n=46) were female. The students' mean cumulative grade point average (CGPA) was 2.69±32. The comparison of the experimental and control groups in terms of gender (p=0.080) and CGPA (p=0.185) revealed that there was no difference between the groups.

There were statistically significant differences between the experimental and control groups in terms of their clinical stress (p=0.006), trait anxiety (p=0.038), state anxiety (p=0.033), and clinical skill (p=0.009) scores. The experimental group's clinical stress, trait anxiety, state anxiety and clinical skill scores were higher than were those of the control group. The comparison of knowledge scores of the groups revealed that there was a difference in favor of the students in the experimental group; however, the difference was not statistically significant (p=0.715) (Table I).

The mean clinical skill score of the students in the experimental group, which was 14.43±7.56 before the training, increased to 17.95±6.48, but the increase was not statistically significant (p=0.054). The case was the same for the mean knowledge level scores. It was 7.69±0.86 before the simulation training, and increased to 8.00±1.59 after the simulation training, but this increase was not statistically significant either (p=0.389) (Table II).

The mean total scores obtained by the students who participated in the simulation training were 3.76±0.78 for the Student Satisfaction and Self-Confidence scale in Learning, 3.97±0.87 for the Simulation Design scale scores, 4.27±0.77 for the Importance of Simulation Design, 3.74±0.69 for the Educational Practices Questionnaire, and 4.14±0.75 for the Importance of Educational Practices. When the students were asked to evaluate the simulation training they had out of 10 points, the mean of the points they gave was 7.21±1.56 (minimum 3 and maximum 10) (Table III).

Discussion

In this present study aimed at investigating the teaching of nursing care skills through simulation use and the effects of the training on care of respiratory diseases, one of the most common health problems in children. Stress and state anxiety levels of the students participating in the simulation training were higher when they started clinical practices. These students' high levels of stress and anxiety may have been due to their high levels of trait anxiety when they started clinical practices. That the stress scores of the students in the experimental group were also high might be related to the fact that the students participating in the simulation training felt that they were expected to achieve better. In the study of Gore et al. (19) (2011), the anxiety levels of nursing students who received simulation training were reported to be significantly lower in their first clinical experience. In their study on the nursing approach to a young child with asthma, Cantrell et al. (9) (2008) found that some of the students experienced stress and performance anxiety during their participation in the clinical simulation training. The simulation training affects the students' anxiety levels either positively or negatively: in some studies, it decreases (19) and in some studies, it increases (9). Keeping in mind the fact that students' anxiety levels during the simulation training can vary will positively contribute to the support provided for them.

The most important result expected from the research was that the student would better perform the clinical skills taught in the simulation training in an actual clinical setting where he/she encountered a real patient. As shown in Table I, the students who participated in the simulation training were more successful in providing the nursing care to a baby with respiratory difficulty. According to the evaluation made during the simulation training, the students in the experimental group were more successful in the actual clinical setting and their clinical skill scores were higher. In LeFlore et al.'s (11) study (2012), knowledge acquisition and healthcare levels of the nursing students who had simulation training on pediatric respiratory diseases (asthma, bronchiolitis, pneumonia and cystic fibrosis) increased significantly. In Kang et al.'s (13) study (2015), a significant increase was observed in nursing

care knowledge of students after simulation training on a child with bronchiolitis was given. Respiratory distress is a condition that makes children feel uncomfortable. Therefore, creating a setting where the scenario brings the patient's reactions to the forefront during the simulation training will increase the students' success levels when they meet an actual patient.

In the present study, there was no difference between the post-simulation knowledge scores of the nursing students in the experimental and control groups. That is probably because they took the same theoretical course. Similarly, there was no difference between the pre-and post-simulation training knowledge scores of the students in the experimental group. In Pauly-O'Neill and Prion's (20) (2013) simulation study on students' skills of drug preparation for pediatric patients, the students' post-intervention knowledge scores were reported as high. In a simulation study conducted by Parker et al. (21) (2011) with undergraduate nursing students who took a Child Health Course, the students' post-simulation training scores were not different from their pre-simulation training scores, similar to this study. Knowledge scores' being influenced by knowledge acquired through the theoretical education was regarded as something expected.

The mean scores the students who participated in the present research obtained from the Student Satisfaction and Self-Confidence scale, Simulation Design scale and Educational Practices Questionnaire, which ranged between 3.76 and 3.97, were above the average. The Importance score given by the students to rate the Simulation Design scale and Educational Practices Questionnaire were over 4 out of 5. It was determined that the students were generally satisfied with their simulation experiences, that they perceived the characteristics of the simulation favorably, and that they thought that simulation training contributed to their development of self-confidence positively. In the literature, the scores obtained in several studies in which the same scales were used were similar (3.45 to 4.40) to those obtained by Cantrell et al. (9) (2008). In many studies, the mean scores obtained from the scales were generally above 4 (22-25). Those studies also emphasized that simulation training increased students' confidence and satisfaction levels (25-27).

When the students were asked to evaluate the simulation training they had out of 10 points, the mean of the points they gave was 7.21±1.56 (Table III). In Doğan's (28) (2015) study conducted with nursing students having simulation training,

Table I. Differences between the experimental and control groups in terms of clinical stress, anxiety, clinical skill and knowledge levels

Post-simulation training clinical practice				
	Experimental group	**Control group**	**Analysis Mann-Whitney U**	**p value**
PAGANA clinical stress score	29.04±9.83	21.88±7.88	223.500	0.006
Trait anxiety score	46.56±5.55	43.58±3.18	255.500	0.038
State anxiety score	46.56±5.55	43.51±3.16	260.000	0.033
Clinical skill Score	17.95±6.48	13.85±5.82	231.000	0.009
Knowledge score	8.00±1.59	7.68±1.45	369.000	0.715

Table II. Comparison of the pre-during and post-simulation training knowledge and clinical skill scores of the experimental group

	Experimental group pre-during the simulation training	**Experimental group post simulation training (in the clinic)**	**Analysis Wilcoxon**	**p value**
Clinical skill scores-(during)	14.43±7.56	17.95±6.48	-1.931	0.054
Knowledge scores-(pre)	7.69±1.86	8.00±1.59	-0.861	0.389

Table III. Evaluations of the students in the experimental group regarding the simulation training

	X ± SD	**Min.**	**Max.**
Student Satisfaction and Self-Confidence scale in Learning score	3.76±0.78	2.08	4.83
Simulation Design scale	3.97±0.87	1.55	6.00
Simulation Design scale (Importance score)	4.27±0.77	1.55	5.00
Educational Practices Questionnaire score	3.74±0.69	1.75	4.63
Educational Practices Questionnaire (Importance score)	4.14±0.75	1.50	5.00
Simulation Training Evaluation score	7.21±1.56	3	10

SD: Standard deviation, Min: Minimum, Max: Maximum

the students rated the contribution of the simulation training at 8.4 points out of 10 when a highly realistic human simulator was used, and 7.9 points when the simulation training was performed with a standard human patient simulator. In another study by Doğan et al. (29) (2016) conducted in 2016, the students who had their training on a moderately realistic pediatric mannequin rated the simulation training at 6.2 points out of 10. When the students assessed the effect of the simulation training on the clinical setting, they gave higher scores in the studies in which highly realistic human simulators were used in the training. Students' expectation from simulation training is that simulators should be highly realistic.

Conclusions

In this present study, because the randomization was realized by means of a lottery method, it was not possible to prevent trait anxiety levels between the groups from being different. Therefore, although it was thought that the high level of state anxiety in the experimental group was due to the increase in the students' awareness, it was not thoroughly evaluated. Thus, it is suggested that trait anxiety scores should also be included in the randomization criteria of future studies.

In conclusion, in this present study, the students' success in the application of clinical skills increased in the group which received the simulation training. Based on this, it is recommended that to tackle the problems encountered especially in critical patient care and child health, simulation training should be widely used.

Key Points

- Simulation training is an effective method of training which enables nursing students to gain skills in a controlled environment.

- Simulation-based training reduces students' risk of misapplication due to lack of experience in becoming prepared for clinical practices.

- Students are more successful in performing interventions in pediatric patients through simulation training in an environment quite similar to actual practice environments.

Ethics

Ethics Committee Approval: This study was approved by the Non-Interventional Clinical Research Ethics Committee of İzmir Katip Çelebi University (approval number: 156/2017).

Informed Consent: Written consent was filled out and given by the students.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: H.Y.S., E.A.A., B.Ö.Ö., A.K., Z.D., P.D., Design: H.Y.S., Data Collection or Processing: E.A.A., B.Ö.Ö., A.K., Z.D., P.D., H.Y.S., Analysis or Interpretation: H.Y.S., E.A.A., A.K., Literature Search: H.Y.S., E.A.A., B.Ö.Ö., A.K., Z.D., P.D., Writing: H.Y.S., E.A.A., B.Ö.Ö., A.K.

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

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References

1. Cant RP, Cooper SJ. Simulation-based learning in nurse education: systematic review. J Adv Nurs 2010;66:3-15.
2. Kapucu S, Bulut H. Turkish nursing students' views of their clinical learning environment: a focus group study. Pak J Med Sci 2011;27:1149-53.
3. Jroundi I, Mahraoui C, Benmessaoud R, et al. Risk factors for a poor outcome among children admitted with clinically severe pneumonia to a university hospital in Rabat, Morocco. Int J Infect Dis 2014;28:164-70.
4. Tanır G, Aytekin C. Çocuklarda alt solunum yolu enfeksiyonları. Sürekli Tıp Eğitimi Dergisi 2001;10:382-5.
5. Le Roux DM, Myer L, Nicol MP, Zar HJ. Incidence and severity of childhood pneumonia in the first year of life in a South African birth cohort: the Drakenstein child health study. Lancet Glob Health 2015;3:95-103.
6. World Health Organization WHO Causes of child mortality. 2015; http://www.who.int/gho/child_health/mortality/causes/en/ Accessed 20 July 2017.
7. Wang H, Liddell CA, Coates MM, et al. Global, regional, and national levels of neonatal, infant, and under-5 mortality during 1990-2013: A systematic analysis for the Global Burden of Disease Study 2013. Lancet 2014;384:957-79.
8. Craver R, Springer J, Begue R. Infections in a children's hospital autopsy population. Fetal Pediatr Pathol 2014;33:135-44.
9. Cantrell MA, Meakim C, Cash K. Development and evaluation of three pediatric-based clinical simulation. Clin Simul Nurs 2008;4:21-8.
10. Sigalet E, Donnon T, Grant V. Undergraduate students' perceptions of and attitudes toward a simulation-based ınterprofessional curriculum. The KidSIM Attitudes Questionnaire. Simul Healthc 2012;7:353-8.
11. LeFlore JL, Anderson M, Zielke MA, et al. Can a virtual patient trainer teach student nurses how to save lives-teaching nursing students about pediatric respiratory diseases. Simul Healthc 2012;7:10-7.
12. Dowson A, Russ S, Sevdalis N, Cooper M, De Munter C. How in situ simulation affects paeditric nurses' clinical confidence. Br J Nurs 2013;22:610-7.
13. Kang KA, Kim S, Kim SJ, Oh J, Lee M. Comparison of knowledge, confidence in skill performance (CSP) and satisfaction in problem-based learning (PBL) and simulation with PBL educational modalities in caring for children with bronchiolitis. Nurse Educ Today 2015;35:315-21.
14. Jeffries PR, Rizzolo MA. Designing and implementing models for the innovative use of simulation to teach nursing care of ill adults and children: a national, multi-site, multi-method study. National League for Nursing and Laerdal Medical, New York, 2006.
15. Unver V, Basak T, Watts P, et al. The reliability and validity of three questionnaires: the student satisfaction and self- confidence

in learning scale, simulation design scale, and educational practices questionnaire. Contemp Nurse 2017;53:60-74.

16. Sendir M, Acaroglu R. Reliability and validity of Turkish version of clinical stress questionnaire. Nurse Educ Today 2008;28:737-43.
17. Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA. Manual for the State-Trait Anxiety Inventory. Palo Alto, CA, Consulting Psychologists Press, 1983.
18. Öner N, Le Compte A. State-Trait Anxiety Inventory Manual. İstanbul, Turkey, Boğaziçi University Press, 1985.
19. Gore T, Hunt CW, Parker F, Raines KH. The effects of simulated clinical experiences on anxiety: Nursing students' perspectives. Clin Simul Nurs 2011;7:175-80.
20. Pauly-O'Neill S, Prion S. Using integrated simulation in a nursing program to improve medication administration skills in the pediatric population. Nurs Educ Perspect 2013;34:148-53.
21. Parker RA, McNeill JA, Pelayo LW, Goei KA, Howard J, Gunter MD. Pediatric clinical simulation: A pilot project. J Nurs Educ 2011;50:105-11.
22. Mills J, West C, Langtree T, et al. Putting it together: Unfolding case studies and high-fidelity simulation in the first-year of an undergraduate nursing curriculum. Nurse Educ Pract 2014;14:12-7.
23. Wang AL, Fitzpatrick JJ, Petrini MA. Comparison of two simulation methods on Chinese BSN students' learning. Clin Simul Nurs 2013;9:207-12.
24. Liaw SY, Scherpbier A, Klainin-Yobas P, Rethans JJ. Rescuing a patient in deteriorating situations (RAPIDS): an evaluation tool for assessing simulation performance on clinical deterioration. Resuscitation 2011;82:1434-9.
25. Swenty CF, Eggleston BM. The evaluation of simulation in a baccalaureate nursing program. Clin Simul Nurs 2011;7:181-7.
26. Golinveaux J, Gerbert B, Cheng J, et al. Oral health education for pediatric nurse practitioner students. J Dent Educ 2013;77:581-90.
27. Lewis DY, Ciak AD. The impact of a simulation lab experience for nursing students. Nurs Educ Perspect 2011;32:256-8.
28. Doğan, P. Hemşirelik eğitiminde farklı simülasyon yöntemlerinin öğrencilerin eleştirel düşünme eğilimlerine ve öz-etkililik düzeylerine etkisi. Unpublished PhD Thesis, İstanbul University, 2015.
29. Doğan Z, Akarsu Ö, Yıldız S, Aydoğan MN, Bircan M. Use of Simulation in Pediatric Nursing Education: nursing students experiences. Eur J Pediatr 2016;175:1393-880. https://www.ncbi.nlm.nih.gov/pubmed/?term=Eur+J+Pediatr+2016%3B175%3A1393-880

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Original Article

Nutritional Habits and Precocious Puberty in Girls: A Pilot Study

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ABSTRACT

Aim: Precocious puberty (PP) is defined as the appearance of secondary sexual characteristics before the age of nine in boys or eight in girls. Due to changing socio-economic conditions, nutritional habits and environmental factors, the onset of normal puberty is being seen at younger ages these days. The purpose of this study was to evaluate the dietary habits and environmental factors in cases that presented to or were being followed up by the Child Endocrinology Clinic with symptoms of PP.

Materials and Methods: The study group included 50 girls aged 2-8 years who presented with symptoms of PP and whose diagnosis was being monitored. A survey noting food consumption was made recording the girls' dietary habits, fast food consumption and frequency, information about their health, physical activity (PA) and environmental factors using a 24-hour-recall technique.

Results: The mean age of the girls was 7.1±0.9 years. According to body mass index z-scores, 62.0% of the girls were overweight [(≥+1 standard deviation (SD)], 34.0% were normal (≥+1 SD - <+1 SD) and 4.0% were underweight. There was a statistically significant difference between the girls' levels of activity and their mean ages ($p<0.05$). The girls' favorite choices of fast food were hamburgers (20.3%), lahmacun (a thin pizza with spicy meat topping) (11.9%), 32% of the girls were using perfumes or skin creams. Plastic culinary utensils were used in 56% of the children's homes. Of those girls who watched more than three hours of television (TV) a day, 71% were overweight.

Conclusion: Increased consumption of fast food containing higher amounts of fat, energy and protein in conjunction with decreased PA, exposure to chemicals that impair the endocrine system and exposure to stimulating devices (TV, computer) may be important factors in the development of PP. Further research is needed to evaluate the negative effects of these factors.

Keywords: Nutritional habits, menarche, obesity, precocious puberty, lifestyle

Introduction

Precocious puberty (PP) is defined as the early onset of puberty with the appearance of secondary sexual characteristics before nine years of age in boys and eight years of age in girls (1).

Paleontological data about the Neolithic age suggests that puberty occurred early in females. This was an evolutionary advantage given the short lifespan during that era, because they were able to reach reproductive capacity quickly. There was an increase in population density and deterioration in hygiene conditions in the period before the Industrial Revolution. This resulted in a delay in the age of menarche, which is the most prominent sign of puberty in females. During the years from the Industrial Revolution to the mid-1900s, the menarche age started occurring earlier most likely due to improved environmental conditions, reduced rates of contagious diseases and easier access to food (2).

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Herman-Giddens et al. (3) analyzed the results of a study performed by North Carolina University (Maternal and Child Health, Public Health School) using the Pediatric Research in Office Settings network and investigating the pubertal development of 17.077 girls between 3-12 years of age. A study in our country reported the prevalent rate of PP in girls between 4-8 years of age was 4.3% (4). It was reported that breasts began to develop and pubic hair began to appear at earlier ages than reported in previous studies of American girls (10.0 years for Caucasian American girls and 8.9 years for Afro - American girls). However, the age of onset for menarche did not change (12.8 years and 12.1 years, respectively). Copenhagen Puberty Research reported a reduction in the age of puberty by up to 12 months in girls from Denmark (5). However, the hypotheses concerning the timing of adolescence are controversial with evidence suggesting that environmental factors play a role in the onset of puberty. Buck Louis et al. (6) reviewed the literature and defined environment as "the sum of all external factors that affect the life, development and survival of an organism". A more extended definition describes environmental factors as non-inheritable factors. Current studies focus on body measurements, nutritional habits and duration of exposure to endocrine impairing chemicals that affect the timing of puberty (7).

Diet is one of the most important factors affecting pubertal development. An adequate, balanced and healthy diet is necessary for all stages of growth and for normal pubertal development. Excessive consumption of processed, high-energy and high-fat food can lead to obesity and PP. Overweight and obese children enter puberty at earlier ages (8).

The aim of this study is to identify the food-related and environmental risk factors that affect the development of PP and to determine their relationship with nutrition in girls that presented to the child endocrinology clinic with signs of PP or who were previously diagnosed with PP and are being monitored.

Materials and Methods

Plan and Methods

Place of Study and Sample Selection

This study included 50 girls aged 2-8 years who presented to the University of Health Sciences, Ankara Child Health and Diseases Hematology Oncology Research and Training Hospital, Department of Pediatric Endocrinology with signs of PP or who had previously been diagnosed with PP. Approval was obtained from the Local Ethics Committee (approval no: 2017/095).

Data Collection

Data for the study group was collected using a structured questionnaire. The questionnaires were filled in by the researcher during one-on-one interviews with the children's parents. The questionnaire provided information about the children's demographic characteristics, their nutritional habits (skipping meals and the reasons for this, consumption of fast food and how often, their most preferred food), information about their health status, and daily food consumption using a 24-hour-recall technique.

Assessment of Dietary Intake and Frequency of Fast Food Consumption

A photographic atlas of food portion sizes was used as a reference in creating a food consumption record using the 24-hour-recall technique in order to determine the girls' nutritional status and their daily levels of energy intake and food consumption (9). Using the 24-hour-recall method, their parents were asked to write down on pre-prepared forms all the food consumed by their daughters over the previous 24 hours.

The frequency table for daily food consumption and fast food consumption recorded the frequency at which the girls consumed food and beverages as follows: daily, 5-6 days a week, 3-4 days a week, 1-2 days a week, once every two weeks, once a month, infrequently and never.

Anthropometric Measurements

The girls' height (cm), weight (kg), waist circumference (cm), upper mid-arm circumference (cm) and skin fold thickness (mm) were measured and recorded on the Anthropometric Measurements Record Form. The anthropometric measurements were taken in the morning while fasting after the girls' shoes and outer clothing were removed. Body weights were measured using SECA brand scales and recorded in kilograms. Height measurements were made with the help of a portable height measuring bar while the girls stood against a wall with their feet together and their heads oriented in the Frankfort plane (eye triangle and ear auricle aligned parallel to the ground). The body mass index (BMI) z-scores determined by age and gender were calculated with the World Health Organization Anthroplus program using the data obtained from the girls' body mass and height measurements. Those who rated +1 SD to +2 SD were considered "slightly overweight" while those rated +2 SD to +3 SD were considered "overweight" and those of +3 SD or higher were considered "extremely overweight" (10). Consent form was filled out by all participants.

Statistical Analysis

The data obtained using the questionnaire were analyzed using the SPSS package program. The food consumption data obtained using the 24-hour-recall method were broken down into nutrient content values using standard meal recipes.

The average daily nutrient amounts per individual were entered into the BEBIS program (11) in order to determine the daily consumption of energy and nutrients. The data obtained were evaluated with respect to the Recommended Dietary Allowances (RDA) (12,13). The intersection points in the evaluation were calculated as recommended daily intake levels [(2/3=67%)±33%]. Consumption of energy and nutrients at 67-133% of RDA was accepted as adequate, <67% was accepted as inadequate and >133% as high. The Student's t-test was used to compare the means between the normally distributed variables in two groups, while the one-way ANOVA test was used to compare the normally distributed variables between three or more groups. Statistical analyses were evaluated at 95% confidence value with $p<0.05$ being considered significant.

Results

This study included 50 girls aged 2-8 years who presented to the University of Health Sciences, Ankara Child Health and Diseases Hematology Oncology Research and Training Hospital, Department of Pediatric Endocrinology with PP symptoms or who had previously received a PP diagnosis. The mean age of the girls was 7.1±0.9 years. There was a significant difference in mean age of the girls in relation to their mothers' education levels ($p<0.05$).

According to BMI z scores, 62.0% of the children were overweight (≥+1 SD), 34.0% were normal (≥+1 SD - <+1 SD) and 4.0% were underweight. In percentile terms 60.0% were overweight (≥85th percentile), 36.0% were normal (≥15th-<85th percentile) and 4.0% were underweight (<15th percentile) (Table I).

In this study, 82% of girls with signs or symptoms of PP or who had been given a PP diagnosis reported that they did not engage in any regular physical activity (PA). The girls engaging in regular PA was 18% which percentage engaged in daily PA was 33.3% and engaged in regular PA 3-4 days a week was 66.7%. Activity was seen to decrease as age increased ($p<0.05$).

When the girls' meal arrangements are examined, it can be seen that 84.0% consume three main meals and three snacks every day, 92.0% do not eat at night while 60.0% eat a final meal/snack between 8.00 and 10.00 p.m. It was determined that 58.0% of the children eat their lunch in 20-30 minutes. Body weight was reported as having increased (64%), decreased (6%) or remained unchanged (30%) over the previous six months.

Some characteristics of the girls with regard to fast food consumption are given in Table II.

64.0% of the girls consumed fast food infrequently, 20.0% consumed fast food 1-2 days per week, 4.0% consumed fast food every day and 12.0% never consumed any fast food.

The fast food types most preferred by the girls are shown in Table III.

According to this, hamburgers (20.3%), pita-lahmacun (11.9%) and grilled chicken in bread (11.3%) were the top three favorite fast foods.

When the energy and nutrients that the girls receive daily are examined according to the reference intervals, it can be seen that 74.0% receive sufficient energy and their intake of carbohydrates (66.0%), calcium (48.0%), folate (58.0%) and vitamin B_6 (46.0%) are also sufficient. Their dietary intake of protein (68.0%), vitamin A (50.0%), vitamin C (44.0%) and vitamin B_{12} (52.0%) are higher than recommended. Iron intake was found to be insufficient in 54.0% of the girls (Table IV).

An examination of other environmental factors that might be instrumental in the development of PP revealed that 32.0% of the girls used perfumes or skin creams. Plastic culinary utensils were used in 56.0% of their homes, 64% of them had a cigarette smoker at home, while some mothers consumed cigarettes (16%) and alcohol (2%) during pregnancy. Analysis of the time spent in front of the television (TV) revealed that the overweight girls watched TV

Table I. Body mass index z-score of the girls

z score and percentiles	s	%
z score		
Underweight (<-1 SD)	2	4.0
Normal (≥-1 SD - <+1 SD)	17	34.0
Overweight (≥+1 SD)	31	62.0

SD: Standard deviation

Table II. Fast food consumption frequency, menu and beverage choices of the girls

Fast food consumption characteristics	s	%
Frequency (n=50)		
Everyday	2	4.0
Once or twice a week	10	20.0
Rarely	32	64.0
Never	6	12.0
Preferences of fast food menu		
Standard menu	18	36.0
One by one select	32	64.0
If the preference is standard menu, selected beverages are... (n=18)		
Cola	7	38.9
Diet Cola	-	-
Yogurt drink/Ayran	8	44.4
Packed fruit juice	2	11.1
Freshly squeezed fruit juice	1	5.6
Carbonated beverage	-	-

for less than an hour a day (76.9%), 2-3 hours a day (11.7%) and 3-4 hours a day (11.2%) with no statistical difference found between them (p>0.05). It was determined that they watched TV mostly at night and that most of them watched TV series.

Discussion

The age at which puberty begins varies depending on genetic features, nutritional status, obesity, stress and environmental factors (14). Signs of puberty are manifesting earlier in children these days and the number of patients presenting to endocrinology clinics due to and diagnosed with PP has also increased. The aim of this study was to identify the nutritional and environmental risk factors affecting PP and to determine if there was any relationship between nutritional habits and children who presented to pediatric endocrinology clinics with signs and symptoms of PP or who had been previously diagnosed with PP.

Puberty refers to a developmental period of rapid and profound change (15). Clinically speaking, puberty in girls is defined as the first appearance of the mammary buds (16). PP is defined as the appearance of secondary sexual characteristics in girls before eight years of age (17). This study included 50 girls aged 2-8 who presented with signs or symptoms of PP or who had previously been diagnosed with PP. Their mean age was 7.1±0.9 years. The mean age of the children increased significantly as the education level of their mothers increased (p<0.05).

The normal age range for the onset of puberty in girls was 8-13 according to cross-sectional data in the 1960s. In Turkish society, the age of onset of puberty was reported to be 10.1±1.0 years for girls (18). Cross sectional data obtained in the United States (US) and Europe in the last two decades report that pubertal milestones are being reached earlier in both sexes (3,19-21).

The signs of PP are advanced bone age, accelerated growth and increased body weight (22). Some modifiable factors such as dietary habits and high adiposity play important roles in the development of PP (23-25). Accordingly, going by their BMI z-scores, (≥+1 SD) 62.0% of the girls were overweight [60% according to percentile values (≥85th percentile)]. A childhood obesity study in our country (26) showed that 21.2% of children aged 7-8 were overweight-obese according to BMI z-scores. This suggests that girls in our country are in a risk group for PP.

Girls and boys who take part in intense PA and exercise were found to have lower BMI and body fat percentage values and later onset of puberty (27). A study involving 3.206 subjects in Colombia detected that menarche age was delayed in girls who perform PA for two hours or more a day (28). In this study, only 18% of the girls with PP were reported as undertaking regular PA. Promoting PA for children with the goal of establishing it as a lifestyle is very important for their general health, psychological status and socializing skills. Specifically, increasing the number of hours for physical education in schools and using these hours actively may help to decrease obesity.

Nutrition is an important factor affecting the timing of puberty. While no single factor is thought to be solely effective, it is believed that the presence of multiple factors can influence the timing of puberty (29). Excessive nutrition

Table III. The most preferred fast food for girls

The most rated fast food	s	%
Hamburger	65	20.3
Lahmacun-Pide	38	11.9
Chicken döner kebab	36	11.3
Pizza	30	9.4
Meat döner kebab	25	7.8
Toast	23	7.2
Turkish bagels	23	7.2
Pastries	19	5.9
Fried potatoes	18	5.6
Shish kebab	15	4.7
Baked potato	8	2.5
Kebab	6	1.9
Turkish pancake	4	1.3
Chicken sandwich	3	0.9
Salad bar	3	0.9
Sandwich	3	0.9
Chicken shish	1	0.3

Table IV. Comparison of energy and nutrient intake of girls by reference intervals

Energy and nutrients	Deficient (<67%)		Adequate (67-133%)		Excess (<133%)	
	s	%	s	%	s	%
Energy	12	24.0	37	74.0	1	2.0
Carbohydrate	5	10.0	33	66.0	12	24.0
Protein	2	4.0	14	28.0	34	68.0
Calcium	19	38.0	24	48.0	7	14.0
Iron	27	54.0	22	44.0	1	2.0
A vitamin	10	20.0	15	30.0	25	50.0
C vitamin	15	30.0	13	26.0	22	44.0
Folate	12	24.0	29	58.0	9	18.0
B_6 vitamin	7	14.0	23	46.0	20	40.0
B_{12} vitamin	11	22.0	13	26.0	26	52.0

and obesity are thought to trigger the onset of puberty. Nutritional status during childhood is thought to be 25% responsible for the early onset of puberty (30). The data obtained during this study from the girls with signs and symptoms of PP and girls who had PP diagnosis showed that 84% regularly consumed three main meals and three snacks a day. Ashwell (31) reported that 13.6% of the girls between 6-11 years of age did not eat breakfast. In this study, only 3% skipped breakfast because they did not want to have breakfast. In fact, a good breakfast reduces the consumption of snacks and energy rich food and therefore helps to manage the body weight of girls with PP who are undergoing treatment.

It takes 20 minutes for the body to feel sated. Therefore, when food is eaten quickly more food is consumed during this time (32,33). In this study, 58.0% of girls took 20-30 minutes to eat their meals. This could create a negative situation in that too much food could be eaten during this time.

It is reported that inadequate and unbalanced nutrition, processed foods and the consumption of foods with high fat and sugar contents may be the cause of the increased incidence in childhood obesity recently and the early onset of puberty in girls (34). One study demonstrated that children are encouraged to consume cheap, easily available snacks that have high energy density and low nutrient values, and that this puts children at risk of early puberty (35). In this study, 20% of the girls with the signs and symptoms of PP or with a PP diagnosis consumed fast food one or two days a week and 64% consumed fast food infrequently (Table II). The most commonly preferred fast foods by the girls were high energy foods such as hamburger (20.3%), lahmacun (11.9%), chicken doner kebab (11.3%), pizza (9.4%), meat doner kebab (7.8%), grilled toast and melted cheese (7.2%), bread rings (7.2%), pastries (5.9%), french fries (5.6%) and shish kebab (4.7%) (Table III).

There is evidence to suggest that the consumption of animal proteins during childhood may be related to PP. A study of children aged 3-8 years in the US found correlations between the consumption of whole animal proteins and early menarche and Age of Peak Height Velocity (APHV) (36). In another study, the consumption of whole and animal-derived protein by 112 boys and girls aged 5-6 years was associated with menarche in girls and voice change in boys. That same study found a link between protein from cow's milk and other dairy products and early pubertal growth and APHV (37). While some studies have suggested a link between animal-derived protein sources and early sexual development, other studies have reported a link between the consumption of plant-based protein sources in childhood and the late onset of puberty. For example, analyses in a study made by Dortmund Nutritional and Anthropometric Longitudinal Design showed that children whose plant-based protein intake was in the lowest one third had earlier APHV than children whose intake was in the highest one third (37). Similarly, Berkey et al. (36) demonstrated a positive correlation between plant-based protein intake and menarche and APHV. The girls in this study consumed a mean of 50.9±20.4 g total protein, 33±18.9 g animal protein and 17.9±6.8 g plant-based protein daily with diet. The mean protein percentage of the daily diet is 15.2±4.1. 68% of the girls consumed more than the required amount of protein and 28% consumed sufficient amounts of protein. The girls' protein consumption was slightly higher than the recommended limits. The interaction with PP may be due to micronutrients, mycotoxins or drugs in the feed given to the animals that provide the protein source.

Previous research on dietary fat and the age of menarche reported a positive relationship between the consumption of fat containing polyunsaturated fatty acids and early menarche and a negative relationship between the consumption of fat containing saturated fatty acids and early menarche (36,38,39). The mean daily fat consumption of the girls in this study was 61.9±21.7 g with 40.1±8.4 g of daily energy being derived from fat. In this study, the percentage of fat-derived energy in daily energy intake was high. It is important that mono and polyunsaturated fats instead of saturated fats are promoted and that they are consumed at the recommended levels. This may prevent both obesity and other health problems associated with obesity.

Kissinger and Sanchez (40) found a positive and statistically significant relationship between iron intake and the age of menarche in 230 girls in the US. Maclure et al. (38) demonstrated that in children with sufficient total energy intake, an increase in vitamin A intake had a strong association with early menarche. In this study, the girls' average daily calcium intake was 634.2±319.2, iron intake was 7.3±2.7 mg and vitamin A intake was 1.080.6±1.829.9 mg. A randomized study of 144 Swiss girls reported that girls who received calcium supplements between 7.9-8.9 years of age reached menarche earlier than girls who did not receive calcium supplements (41). In our study, 48.0% of the girls received adequate amounts of calcium, 54% received inadequate amounts of iron and 50% received excessive amounts of vitamin A. Animal-derived protein sources should be promoted in order to increase children's iron intake while milk and dairy products should be promoted in order to increase calcium intake.

Bisphenol A (BPA), an estrogenic compound used in food and beverage packaging, has been associated with late puberty in several studies. Phthalates, which are used for food packaging, have been associated with early menarche in girls (42). An analysis of 2003-2010 National Health and Nutrition Examination Survey data on 987 adolescent girls aged 12-19 years found that girls with moderate BPA levels were less likely to experience early menarche than girls with low BPA levels. They suggested that BMI may have changed the relationship between menarche and BPA (43). A

cross-sectional study investigated the associations between exposure to phthalate and sexual maturation in 725 girls aged 6-19 years in Denmark. The researchers found that the girls in the highest quarter for exposure to mono-n-butyl phthalate + mono-isobutyl phthalate and monobenzyl phthalate reached stage 2 of pubic hair development at a later age than girls in the lower quarters (44).

In this study, 56% of their parents reported using plastic culinary utensils at home. 60.0% of the children drink water out of plastic bottles, 6.0% rarely do so and 34.0% do not. 70.0% of the families used plastic bottles/jugs for water consumption. Most of the families used high amounts of plastic products and packaged products. An analysis of the consumption of snack foods revealed that 98% of the girls did not consume these products. These endocrine spoilers stimulate the hypothalamo-hypophyseal-gonadal axis and cause shifts in the age of puberty. For this reason, parents should be informed about this topic. In short, we suggest that materials used for food packaging should be health-friendly and should not cause health problems.

Time spent in front of visual media like TV, computers, tablets etc. is an important risk factor for obesity. Also, the visual and sexual content of the programs watched may accelerate the puberty process and may cause emotional confusion with respect to sexuality (45). Analysis of the time spent in front of the TV revealed that the overweight girls watched TV for less than an hour a day (76.9%), 2-3 hours a day (11.7%) and 3-4 hours a day (11.2%) with no statistical difference found between them ($p>0.05$).

Study Limitations

The small number of subjects due to the limited time period is one of the factors that limited our work. Moreover, the use of a control group in addition to a study group would have made the study's results more significant and accurate. In order for future studies examining the effects of nutrition on puberty to give more significant results, study groups should be divided into newly diagnosed patients and follow-up patients because once diagnosis has been made, the families' awareness increases resulting in changes to their children's dietary habits.

Conclusion

Changing lifestyles and habits in all aspects of society have led to an increase in the number of children with PP. In girls with PP, particularly when they are treated for more than a year, the importance of maintaining the ideal bodyweight should be emphasized. Consistent nutritional training, methods to increase the intensity and duration of PA and maintaining regular meal times are important factors in the dietary management of obesity. Physicians should monitor these children regularly and give nutritional counseling. Since children use their parents as role models, the girls' nutritional habits are also similar to their parents' habits. In order to advance the age of puberty, families should be educated about their children's nutritional habits and PA status. Advising girls with PP to modify their eating habits such as having breakfast, eating less food at mealtimes and eating more slowly is important in that it prevents obesity by promoting healthy eating habits.

Further research with a larger cohort is required to determine the effects of nutrition on puberty.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Ankara Child's Health and Diseases Hematology Oncology Training and Research Hospital Local Ethics Committee (approval number: 2017/095).

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

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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References

1. Carel JC, Lahlou N, Roger M, Chaussaın JL. Precocious puberty and statural growth. Hum Reprod Update 2004;10:135-47.
2. Gluckman PD, Bergstrom CT. Christmas 2011: Food for Thought: Evolutionary biology with in medicine: a perspective of growing value. BMJ 2011;343:4-8.
3. Herman-Giddens ME, Slora EJ, Wasserman RC, et al. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings network. Pediatrics 1997;99:505-12.
4. Atay Z, Turan S, Guran T, Furman A, Bereket A. The prevalence and risk factors of premature thelarche and pubarche in 4 to 8 year old girls. Acta Paediatr 2012;10:71-5.
5. Aksglaede L, Sorensen K, Petersen JH, Skakkebæk NE, Juul A. Recent decline in age at breast development: the Copenhagen Puberty Study. Pediatrics 2009;123:932-9.
6. Buck Louis GM, Gray LE Jr, Marcus M, et al. Environmental factors and puberty timing: expert panel research needs. Pediatrics 2008;121(Suppl 3):192-207.
7. Euling SY, Herman-Giddens ME, Lee PA, et al. Examination of US puberty-timing data from 1940 to 1994 for secular trends: panel findings. Pediatrics 2008;121(Suppl 3):172-91.

8. Soliman A, De Sanctis V, Elalaily R. Nutrition and Pubertal Development. Indian J Endocrinol Metab 2014;18(Suppl 1):39-47.
9. Rakicioglu N, Tek Acar N, Ayaz A, et al. Yemek ve besin fotoğraf kataloğu ölçü ve miktarlar. Hacettepe Üniversitesi Beslenme ve Diyetetik Bölümü. Ankara, Ata Ofset Matbaacılık, 2015
10. World Health Organization. 2013. Obesity. http://www.who.int/ topics/obesity/en/.
11. BEBİS. Bebis Nutrition Data Base. The German Food Code and Nutrient Data Base (BLS II.3, 1999) with additions from USDA-sr and other sources, İstanbul, Turkey, 2004.
12. NAP. National Academy Press. Nutrient Adeqency-Asessment Using Food Consumption Surveys. Washington D.C, 1986:14.
13. Pekcan G. Beslenme durumunun saptanması. T.C. Sağlık Bakanlığı Temel Sağlık Hizmetleri Genel Müdürlüğü Beslenme ve Fiziksel Aktiviteler Daire Başkanlığı, Sağlık Bakanlığı. Ankara, Klasmat Matbaacılık, 2008.
14. Kletter GB, Klein KO, Wong YY. A pediatrician's guide to central precocious puberty. Clin Pediatr (Phila) 2015;54:414-24.
15. Golub MS, Collman GW, Foster PM, et al. Public health implications of altered puberty timing. Pediatrics 2008;121:218-30.
16. Parent AS, Teilmann G, Juul A, Skakkebaek NE, Toppari J, Bourguıgnon JP. The timing of normal puberty and the age limits of sexual precocity: variations around the world, secular trends, and changes after migration. Endocr Rev 2003;24:668-93.
17. Carel JC, Leger J. Precocious puberty. N Engl J Med 2008;358:2366-77.
18. Bundak R, Darendeliler F, Günöz H, Baş F, Saka N, Neyzi O. Puberty and pubertal growth in healthy Turkish girls: no evidence for secular trend. J Clin Res Pediatr Endocrinol 2008;1:8-14.
19. Aksglaede L, Sorensen K, Petersen JH, Skakkebæk NE, Juul A. Recent decline in age at breast development: the Copenhagen Puberty Study. Pediatrics 2009;123:932-9.
20. Roelants M, Hauspie R, Hoppenbrouwers K. References for growth and pubertal development from birth to 21 years in Flanders, Belgium. Ann Hum Biol 2009;36:680-94.
21. Biro FM, Greenspan LC, Galvez MP, et al. Onset of breast development in a longitudinal cohort. Pediatrics 2013;132:1019-27.
22. Çatlı G, Erdem P, Anık A, Abacı A, Böber E. Clinical and laboratory findings in the differential diagnosis of central precocious puberty and premature thelarche. Turk Pediatri Ars 2015;50:20-6.
23. Maisonet M, Christensen KY, Rubin C, et al. Role of prenatal characteristics and early growth on pubertal attainment of British girls. Pediatrics 2010;126:591-600.
24. Cheng G, Buyken AE, Shıı L, et al. Beyond overweight: nutrition as an important lifestyle factor influencing timing of puberty. Nutr Rev 2012;70:133-52.
25. Salgin B, Norris SA, Prentice P, et al. Even transient rapid infancy weight gain is associated with higher BMI in young adults and earlier menarche. Int J Obes (Lond) 2015;39:939-44.
26. Çocukluk Çağı Obezite Araştırması-2013 (COSI-TR-2013). Erişim adresi: http://www.diabetcemiyeti.org/var/cdn/a/f/cosi-tr-sonuclari.pdf
27. Buchan DS, Ollis S, Young JD, et al. The effects of time and intensity of exercise on novel and established markers of CVD in adolescent youth. Am J Hum Biol 2011;23:517-26.
28. Chavarro J, Villamor E, Narvaez J, Hoyos A. Socio-demographic predictors of age at menarche in a group of Colombian university women. Ann Hum Biol 2004;31:245-57.
29. Fısher MM, Eugster EA. What is in our environment that effects puberty? Reprod Toxicol 2014;44:7-14.
30. Karlberg J. Secular trends in pubertal development. Horm Res r 2002;57(Suppl 2):19-30.
31. Ashwell M. An examination of the relationship between breakfast, weight and shape. Br J Nurs 2010;19:1155-9.
32. Cho KY, Park H, Seo JW. The relationship between lifestyle and metabolic syndrome in obese children and adolescents. Korean J Pediatr Gastroenterol Nutr 2008;11:150-9.
33. Hassink SG; Pediatric Expert Panel. Weighing risk: the expert committee's recommendations in practice. Semin Pediatr Surg 2009;18:159-67.
34. Proos L, Gustafsson J. Is early puberty triggered by catch-up growth following undernutrition? Int J Environ Res Public Health 2012;9:1791-809.
35. Moffat T. The "childhood obesity epidemic": health crisis or social construction?. Med Anthropol Q 2010;24:1-21.
36. Berkey CS, Gardner JD, Frazier AL, Colditz GA. Relation of childhood diet and body size to menarche and adolescent growth in girls. Am J Epidemiol 2000;152:446-52.
37. Günther AL, Karaolis-Danckert N, Kroke A, Remer T, Buyken AE. Dietary protein intake throughout childhood is associated with the timing of puberty. J Nutr 2010;140:565-71.
38. Maclure M, Travis LB, Willett W, Macmahon B. A prospective cohort study of nutrient intake and age at menarche. Am J Clin Nutr 1991;54:649-56.
39. Rogers IS, Northstone K, Dunger DB, Cooper AR, Ness AR, Emmett PM. Diet throughout childhood and age at menarche in a contemporary cohort of British girls. Public Health Nutr 2010;13:2052-63.
40. Kissinger DG, Sanchez A. The association of dietary factors with age at menarche. Nutr Res 1987;7:471-9.
41. Chevalley T, Rizzoli R, Hans D, Ferrari S, Bonjour JP. Interaction between calcium intake and menarcheal age on bone mass gain: an eight-year follow-up study from prepuberty to postmenarche. J Clin Endocrinol Metab 2005;90:44-51.
42. Zhang Y, Cao Y, Shi H, et al. Could exposure to phthalates speed up or delay pubertal onset and development? A1.5-year follow-up of a school-based population. Environ Int 2015;83:41-9.
43. Mcguinn LA, Ghazarian AA, Joseph Su L, Ellison GL. Urinary bisphenol A and age at menarche among adolescent girls: evidence from NHANES 2003-2010. Environ Res 2015;136:381-6.
44. Frederiksen H, Sorensen K, Mouritsen A, et al. High urinary phthalate concentration associated with delayed pubarche in girls. Int J Androl 2012;35:216-26.
45. Brown JD, Halpern CT, L'Engle KL. Mass media as a sexual super peer for early maturing girls. J Adolesc Health 2005;36:420-7.

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Original Article

Prevalence of Febrile Seizures in School-Aged Children: A Community Based Survey in İzmir, Turkey

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ABSTRACT

Aim: Febrile seizures (FS) are the most common seizures seen in childhood. Although they are usually benign and self-limiting, parents feel great fear and concern about them. The prevalence of FS varies in different parts of the world. These differences are thought to be due to genetic, geographic and environmental factors. However, there has been no recent study about the prevalence of FS among Turkish children. This study was designed to find out the prevalence, clinical and some epidemiological features of FS among Turkish school children.

Materials and Methods: A school based, cross-sectional study was conducted in first and second grade children. A stratified cluster sampling technique was used to define the study population, which represents the schools located in the metropolitan area of İzmir. Data were collected through a standard questionnaire from the parents who agreed to be involved in the study. The survey had questions about some demographic features of the children and FS episodes.

Results: Three thousand eighty hundred six children and parent pairs agreed to participate in the survey. The FS prevalence determined was 4.8% (boys, 5.2%; girls, 4.3%, p>0.05). It was found that 28.5% of the children experienced their first FS between the ages of 18 months and three years old and most of them had an upper respiratory tract infection. The most common practice by parents during the seizure was admission to the nearest emergency room. The recurrence rate for FS was 33.0%.

Conclusions: The FS prevalence determined in our study is lower than previous studies in Turkey. It was thought that the advancing healthcare systems in our country might have decreased the FS prevalence within the last eight years in Izmir.

Keywords: Children, febrile seizure, fever, prevalence, seizure

Introduction

Febrile seizures (FS) are the most common seizures that occur with a temperature of 38 ºC or higher in the absence of a history of prior a FS. It is seen with afebrile illness not caused by a central nervous system infection or any metabolic imbalance. FS are usually seen between the ages of 6 and 60 months (1-3). According to the literature, there are no cognitive adverse effects of having FS. These patients do not have any increased risk of abnormalities of attitude, attention or school performance compared with age-matched controls (2). Although FS are usually benign and self-limiting, parents feel great fear and concern about them. Also, the risk of epilepsy after FS increased between 3% to 7% compared with nearly 0.5% of the general population which makes FS a significant health problem (4,5).

Methodological differences might be a factor, but the prevalence of FS varies in different parts of the world (2). Higher prevalences are found in Japan and Guam (8% and 14%, respectively), whereas, the prevalence in Europe and

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United States is reported between 2% and 6.9% (6-9). The prevalence of FS in Turkey was found to be between 3.5% and 12.8% in previous studies (10-15). These differences are thought to be due to genetic, geographic and environmental factors. Also, due to socio-economic and environmental factors of population change through time, the prevalence of FS might have changed. However, there has been no recent study about the prevalence of FS among Turkish children.

The objective of this study is to find out the prevalence, clinical and some epidemiological features of the FS among Turkish children aged from 6 to 7 in the center of İzmir city.

Materials and Methods

A cross-sectional study was conducted in first and second grade primary school children in the metropolitan area of İzmir. Information on the study population was obtained from the Bureau of Statistics of the Provincial Education Administration of İzmir (16). The primary school grade 1 and 2 population consisted of 65.866 children in 2015 in İzmir. Taking into consideration the prevalence rate detected by Aydin et al. (15) in 2008 of 9.7%, with ±1 standard deviation (SD) with a 99% confidence interval, we planned to assess 5.340 students for this study. Nine districts in İzmir city center were the clusters for our study, and a cluster-sampling method was used. Randomly chosen schools from the sample frame were represented proportionally to their size. Taking into account those questionnaires that would not be replied and returned, instead of 5.340, we distributed 5.501 questionnaires. Together with the questionnaire, a consent/approval form was sent to the families of the sample population.

After Dokuz Eylül University Ethics Committee (approval number: 2015/28-15) was received, written permission was obtained from the Provincial Education Administration and Governor of İzmir City and then the study was performed.

We planned to collect data for our study via the questionnaire to be answered by the parents of first and second grade students in the 2015-2016 educational year. The survey, which had 30 questions, was prepared according to the guidelines for epidemiologic studies on epilepsy, which were proposed by the Commission on Epidemiology and Prognosis, International League Against Epilepsy in 1993, and also according to the current literature about epilepsy. To minimize any memory difficulties, we added an option as "I do not remember" to the survey and these data were accepted as missing data. Teachers sent questionnaires to the parents, who were asked to return them within five days via the children. The response rate was 69.2%, and 3.806 questionnaires were returned out of 5.501 sent.

The survey had questions about some demographic features of the children and FS episodes. The main independent variables of the study were age and gender of children, the FS history of children, the reason for fever, type of treatment conducted by the parents during the FS, admission to a medical unit, the medicine recommended and also a story of FS and epilepsy throughout the family.

FS were defined as seizures that occur in children aged between six months and six years, accompanied by a fever (at least 38 °C before the onset of the seizure) without signs of an intracranial infection (3). Cases with intracranial infections such as encephalitis or meningitis, or intoxication as a reason for the fever, and those who had a history of an afebrile seizure were excluded from the study.

Data were analyzed using SPSS version 21.0 for Windows software (SPSS Inc., Chicago, IL). Results were reported as mean ± SD values or n (%) where appropriate. The statistical significance level was set at a p value <0.05. The normality of data distribution was checked using the Kolmogorov–Smirnov test in the whole group and the subgroups. Statistical analysis was done by using t-test for measurable variables and $\chi 2$ test for countable variables.

Results

Of the sent 5.501 questionnaires, parents of 3.806 voluntarily completed and returned the survey (69.2%). Out of 3.806 cases, 30 were excluded from the study due to the diagnosis of intoxication, encephalitis, meningitis and history of afebrile seizure. Finally, 3.776 cases were assessed, 49.3% of them were boys. The median age of the children at the time of the survey was 7.0 years (range 5.0 to 8.5). Of the 3.776 investigated children, 181 (4.8%, 95% confidence interval 4.1% to 5.5%) were reported to have experienced at least one FS. Among them, 98 were boys and 83 were girls. Some demographic characteristics are shown in Table I. We found a slightly higher prevalence of FS in boys compared to girls (5.2% and 4.3%, respectively), but this was not significantly significant (p=0.183). The FS prevalence in six-

Table I. Some demographic characteristics of study population

Demographic characteristics	n (%)
Age, months	
Mean ± SD	6.5 (±0.61)
Median	7
Gender	
Males	1.862 (49.3)
Females	1.914 (50.7)
Febrile seizure history	
Overall	181 (4.8)
Males	98 (5.2)
Females	83 (4.3)

SD: Standard deviation

Table II. Febrile seizure characteristics		
	n	**%**
Febrile seizure age		
6-11 months	21	11.7
12-17 months	37	20.7
18-35 months	51	28.5
3-4 years	40	22.3
>4 years	30	16.8
Fever		
38-39 ºC	103	57.0
>39 ºC	78	43.0
Time between fever and seizure		
≤30 minutes	43	35.6
31-60 minutes	33	27.2
1-23 hours	37	30.6
≥24 hours	8	6.6
Reason for the fever		
Acute tonsillopharyngitis	140	80.5
Otitis media	16	9.2
Acute gastroenteritis	16	9.2
Unknown	2	1.1
Number of febrile seizure episodes		
1 episode	120	67.0
2 episodes	39	21.8
≥3 episodes	22	11.2
Recommended medicine type		
Medicine to be used on the fever	73	71.6
Antiepileptic drugs for long term treatment	15	14.7
Medicine to be used at the time of seizure	14	13.7

There are 2 missing data from the febrile seizure age data, 60 missing data from the time between fever and seizure data, 7 missing data from the reason for the fever data and 9 missing data from the recommended medicine Type

year-old students was lower than in seven years old students (4.1% and 5.3%, respectively), but this difference was not statistically significant (p=0.105).

Our results showed that 28.5% of the children experienced their first FS between the ages of 18 months and three years old. Among children who had a FS history, 62.8% of them had a seizure within the first hour of the fever. Most of the parents report that their children had an upper respiratory tract infection as the reason for the fever, and 12.4% of them had a vaccination history at two weeks before the seizure. 94.4% of the parents (171/181) brought their child to the hospital, and medicine was recommended for 54.0% of those (Table II). Sixty-one (33%) children were reported to have experienced two or more FS episodes. 37.3% of the patients with recurrent FS had their first episode before 18 months of age. The first episode age did not significantly affect the recurrence risk for FS (p=0.327). 59.3% of the repeated cases were males, and there was no significant difference between males and females in recurrence risk (p=0.284).

The most common practices by parents during the seizure were admission to the nearest emergency room and giving a shower to the child in order to decrease the fever. (Table III). Only 4.4% of them turned the child's head to the right or left side to open the airway. One parent attempted to perform cardiopulmonary resuscitation. There was no significant difference in attitudes between parents with single FS and multiple FS (p>0.05).

Seizure history among family members of FS subjects is shown in Table IV. Among the 181 FS subjects, 29.0% of them gave a history of FS for their parents. Approximately 20% of them had a history of convulsive disorders within their immediate family and relatives.

Discussion

FS is the most common type of childhood seizure disorders. Most cases of FS are benign and self-limiting, and in general, treatment is not recommended (2). Our study was a school-based, cross-sectional prevalence survey of a history of FS in children between the ages of 6 and 7 in İzmir.

Table III. Attitudes of the parents during the febrile seizure (n=181)							
	Total		**Single FS**		**Multiple FS**		**p value**
	n	**%**	**n**	**%**	**n**	**%**	
Admission to the nearest emergency department	114	63.0	78	65.0	36	61.0	0.722
Giving a shower to the child to decrease the fever	53	29.3	31	25.8	22	37.3	0.160
Using wet clothes to decrease the degree of fever	15	8.3	8	6.7	7	11.9	0.381
Giving the medicine advised before	13	7.2	6	5.0	7	11.9	0.097
Call to the emergency service (112)	9	5.0	6	5.0	3	5.1	0.981
Positioning the patient (Turning the child's head to the right or left side)	8	4.4	4	3.3	4	6.8	0.507

Some parents carried out more than one action. FS: Febrile seizure

The prevalence of FS in our study was found to be 4.8%. Our result is similar to the literature from Western countries (2,6-9) while our prevalence rate is lower than Asian and African countries (17-20). The cause for higher prevalence rates in Asian and African countries is not known. It is hypothesized that it may be due to a different genetic predisposition as well as the influence of environmental factors (21). FS prevalence rates in our country were reported as 4.5% and 3.5% in two previous studies which are similar to our result (11,14). On the other hand, the prevalence rate in primary school children in Diyarbakır was found to be 8.9% (12). We found a lower prevalence rate compared to the study by Aydin et al. (15) in which the prevalence was 9.7% in İzmir. Moreover, in another study, researchers reported the FS prevalence as 12.8% in İzmir (22). These differences might be due to methodological variations between studies. Also, the reduction in the prevalence of FS within the similar population, like our study and the study by Aydin et al. (15), may be partly as a result of the improved education of parents' behaviors towards a child with fever. Unfortunately, we did not have any information about parents' fever attitudes in our study.

There were some studies that found that males have a slightly higher frequency of FS (male to female ratio, 1.1:1 to 2:1) (2,20). Like these studies, there were more boys than girls with FS, 1.2:1 in our study (17,20,23-25). There is no explanation for this male predominance, but some researchers considered that boys have a predisposition to the febrile illnesses that may cause FS (2,9,17,19). On the other hand, this prevalence rate difference between boys and girls was not statistically significant in our study like most other studies (2,17).

In our study, we found that FS was mostly seen at the ages between 18 months and 3 years, similar to the contemporary literature (17,19,20,26). We also found that most of the FS cases had a fever of 39 °C or more and seizure occurred within the first hour of the fever. These findings are similar to the previous studies (2,7,9,18-20). In our study, the most common reason of the fever among the FS cases was upper respiratory tract infections. Studies from the Western world, Japan, and our neighbors found similar results (5-8,18,27,28). On the other hand, bacterial meningitis and severe falciparum malaria were the most common infections found in FS cases in Africa (17). FS may recur in approximately 30% of the cases with a first episode, and we found a similar FS recurrence rate to the contemporary literature (2,18,20).

Table IV. Family seizure histories of febrile seizure subjects

		n	Percentages
Febrile seizure history of parents	+	52	29.0%
	-	127	71.0%
Febrile seizure history of siblings	+	24	13.4%
	-	155	86.6%
Afebrile seizure history of parents	+	5	2.8%
	-	174	97.2%
Afebrile seizure history of siblings	+	3	1.7%
	-	176	98.3%
Febrile and/or afebrile seizure history of other family members	+	28	15.7%
	-	150	84.3%

Among the 181 cases with febrile seizure histories, there are 2 missing data in the variables that were questioned for febrile seizure history of parents and siblings, and 3 missing data in the other family members

A significantly increased risk for FS was found for children of whom there was a history of FS in the parents or/and siblings (2,9). According to the literature, 25% to 40% of the cases had a positive family history for FS (2,29). 29% of the parents and 13.4% of the siblings had a history of FS in our study. A family history of FS is considerably higher among FS cases in our study, and this is concordant with the literature.

Although FS is one of the benign diseases seen in childhood, parents can perceive FS as a traumatic and highly dangerous event. It is essential to reduce parental concerns to improve their responses to FS at home. Parental attitudes toward FS are important for children's first aid during the seizure. Sixty-three percent of parents brought their child directly to the hospital in our study. In a similar study in Japan, 91% of parents brought their child directly to the hospital by ambulance after an emergency call (30). Also, in Korea it is found that during a FS, 86.5% of the parents rushed the child to an emergency department (31). These results show us that although parental FS knowledge has significantly improved, most parents still panic and rush their child to doctors without giving first aid to the child. Only 4.4% of them turned the child's head to the right or left side to open the airway. In our study, this result did not change between parents who have children with a single FS and parents who have children with recurrent FS. According to our results, although most parents had thought that they had an appropriate approach during the seizure of their children, most of them had false or insufficient information about seizure management at home. These results might be due to an inappropriate education of parents or a variation in the quality of information given by health care professionals in İzmir.

Study Limitations

We have several limitations. Firstly, our study was carried out as a school-based survey. Data was collected by questionnaire. There was no clinical evaluation. Therefore, febrile reactions might have been perceived as a FS by parents. Secondly, because we used a questionnaire method, recall bias might have interfered with the results. On the other hand, a population-based questionnaire method remains the most practical method for assessing these parameters in large groups. Moreover, to reduce recall bias, we did this study on 6-7 years old children. Thirdly, although schooling

until the 8th grade is obligatory in Turkey, some low-income families do not send their children to school. They choose to send them to work, and this might affect the results. Along with that, use of a school-based questionnaire method enabled us to find cases who could not access health care facilities because of social, cultural or financial problems. So, due to this, we thought that our study design enabled us to find more realistic results on the prevalence of FS.

Conclusion

In conclusion, the FS prevalence determined in our study is lower than the study within a similar population done by Aydin et al. (15) in 2008. Our study supports findings that the prevalence of FS in our country is similar to developed countries but lower than the developing Asian communities. It was thought that increasing the awareness of febrile illness of parents and the advancing healthcare systems in our country may have decreased the FS prevalence within the last 8 years in İzmir. Our school-based population study enabled us to know the prevalence rate of FS, but repeated studies are needed to follow-up the effect of changing socio-economic factors on FS prevalence.

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Ethics

Ethics Committee Approval: The study was approved by the Dokuz Eylül University Local Ethics Committee (approval number: 2015/28-15).

Informed Consent: Written and verbal consent was obtained from the patients who participated in this study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: M.A., T.İ., A.E., A.A., Design: M.A., D.L., A.A., Data Collection or Processing: M.A., D.L., T.İ., Analysis or Interpretation: T.İ., D.L., A.E., A.A., Literature Search: M.A., T.İ., Writing: M.A., T.İ.

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

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References

1. No authors listed. Guidelines for epidemiologic studies on epilepsy. Commission on Epidemiology and Prognosis, International League Against Epilepsy. Epilepsia 1993;34:592-6.
2. Mikati MA. Febrile Seizures. In: Kliegman RM, Stanton BF, St Geme JW, Schor NF, Behrman RE (eds). Nelson Textbook of Pediatrics, 19th ed. Philadelphia, Elsevier, 2011;2017-9.
3. Steering Committee on Quality Improvement and Management, Subcommittee on Febril Seizures American Academy of Pediatrics. Febril seizures: clinical practice guideline for the long-term management of the child with simple febril seizures. Pediatrics 2008;121:1281-6.
4. Annegers JF, Hauser WA, Shirts SB, Kurland LT. Factors prognostic of unprovoked seizures after febrile convulsions. N Engl J Med 1987;316:493-8.
5. Forsgren L, Heijbel J, Nyström L, Sidenvall R. A follow-up of an incident case-referent study of febrile convulsions seven years after the onset. Seizure 1997;6:21-6.
6. Verity CM, Butler NR, Golding J. Febrile convulsions in a national cohort followed up from birth. I-Prevalence and recurrence in the first five years of life. Br Med J (Clin Res Ed) 1985;290:1307-10.
7. Vestergaard M, Christensen J. Register-based studies on febrile seizures in Denmark. Brain Dev 2009;31:372-7.
8. Sillanpää M, Camfield P, Camfield C, et al. Incidence of febrile seizures in Finland: prospective population-based study. Pediatr Neurol 2008;38:391-4.
9. Hauser WA. The prevalence and incidence of convulsive disorders in children. Epilepsia 1994;35(Suppl 2):1-6.
10. Gökyiğit A, Çalışkan A. İstanbul tıp fakültesi son sınıf öğrencilerinde febril konvülsiyon prevalansı. Tıp Fak Mecmuası 1985;48:102-7.
11. Okan N, Okan M, Eralp O, Aytekin AH. The prevalence of neurological disorders among children in Gemlik (Turkey). Dev Med Child Neurol 1995;37:597-603.
12. Yayla V, Çakmak G, Apak I, Ate U, Erdoğan F. İlkokul çocuklarında geçirilmiş febril konvulziyon prevalansı. Yeni Symposium 1997;35:11-3.
13. Aydin A, Ergor A, Ergor G, Dirik E. The prevalence of epilepsy amongst school children in İzmir, Turkey. Seizure 2002;11:392-6.
14. Yakinci C, Kutlu NO, Durmaz Y, Karabiber H, Eğri M. Prevalence of febril convulsion in 3637 children of primary school age in the province of Malatya, Turkey. J Trop Pediatr 2000;46:249-50.
15. Aydin A, Ergor A, Ozkan H. Effects of sociodemographic factors on febrile convulsion prevalence. Pediatr Int 2008;50:216-20.
16. Annual Reports: Educational Background of İzmir. İzmir State Education Department; Research, Planning and Statistics Unit: (2014-2015). State Education Publishing, İzmir, 2016.
17. Assogba K, Balaka B, Touglo FA, Apetsè KM, Kombaté D. Febrile seizures in one-five aged infants in tropical practice: Frequency, etiology and outcome of hospitalization. J Pediatr Neurosci 2015;10:9-12.
18. Shinnar S, Glauser TA. Febrile seizures. J Child Neurol 2002;17(Suppl 1):44-52.
19. Sugai K. Current management of febrile seizures in Japan: an overview. Brain Dev 2010;32:64-70.
20. Chung S. Febrile seizures. Korean J Pediatr 2014;57:384-95.
21. Berg AT, Shinnar S, Darefsky HT, et al. Predictors of recurrent febrile seizures. A prospective cohort study. Arch Pediatr Adolesc Med 1997;151:371-8.
22. Çelikkol B. Sistemic lupus erythematosus prevalence in İzmir (Dissertation). Department of Pediatrics, Dokuz Eylül University School of Medicine, Turkey, 1999.
23. Forsgren L, Sidenvall R, Blomquist HK, Heijbel J. A prospective incidence study of febrile convulsions. Acta Paediatr Scand 1990;79:550-7.
24. Hwang G, Kang HS, Park SY, Han KH, Kim SH. Predictors of unprovoked seizure after febrile seizure: short-term outcomes. Brain Dev 2015;37:315-21.
25. Nilsson G, Fernell E, Arvidsson T, Neville B, Olsson I, Gillberg C. Prevalence of febrile seizures, epilepsy, and other

paroxysmal attacks in a Swedish cohort of 4-year-old children. Neuropediatrics 2016;47:368-73.

26. Sadleir LG, Scheffer IE. Febrile seizures. BMJ 2007;334:307-11.
27. Bethune P, Gordon K, Dooley J, Camfield C, Camfield P. Which child will have a febrile seizure? Am J Dis Child 1993;147:35-9.
28. Delpisheh A, Veisani Y, Sayehmiri K, Fayyazi A. Febrile seizures: etiology, prevalence, and geographical variation. Iran J Child Neurol 2014;8:30-7.
29. Greenberg DA, Holmes GL. The genetics of febrile seizures. In: Baram TZ, Shinnar S (eds). Febrile seizures. San Diego, Academic Press, 2002:249-61.
30. Kanemura H, Sano F, Mizorogi S, Tando T, Sugita K, Aihara M. Parental thoughts and actions regarding their child's first febrile seizure. Pediatr Int 2013;55:315-9.
31. Huang MC, Liu CC, Huang CC, Thomas K. Parental responses to first and recurrent febrile convulsions. Acta Neurol Scand 2002;105:293-9.

Febrile Seizure Prevelance Survey

No:
Person filling out the survey: Mother Father
1. Birth date of your child:
2. Sex: Boy Girl

3. Does your child have a disease that requires constant medication?
a. Yes: .....
b. No

4. Did your child have a febrile seizure?
a.Yes
b. No
c. I don't remember
5. If your answer is yes, please continue the survey, otherwise the survey ends here

6. How old was your child when he/she had a febrile seizure?
a. 6-11 months
b. 12-17 months
c. 18-35 months
d. 3-4 years
e. >4 years

7. What was the temperature of your child during the febrile seizure?
..... ºC

8. What was the time between fever and febrile seizure of your child?
a. ≤ 30 minutes
b. 31-60 minutes
c. 1-23 hours
d. ≥24 hours

9. Had your child been vaccinated within the previous 2 weeks before the febrile seizure?
a. Yes
b. No
c. I don't remember

10. What did you do first when your child had a seizure?
a. Admission to the nearest emergency department
b. Giving a shower to the child to decrease the fever
c. Using wet clothes to decrease the degree of fever
d. Giving the medicine advised before
e. Call to the emergency service (112)
f. Positioning the patient (Turning the child's head to the right or left side)

11. What was the reason of your child's fever?
a. Acute tonsillopharyngitis
b. Otitis media
c. Acute gastroenteritis
d. Urinary tract infection
e. Vaccination
f. Other:.....
g. I don't remember

12. Was there any medicine recommended to be used for your child?
a. Medicine to be used on the fever
b. Antiepileptic drugs for long term treatment
c. Medicine to be used at the time of seizure
d. No
e. I don't remember

13. How many times did your child have a febrile seizure?
a. One
b. More than one: .....(please write)

14. Has your child previously had a seizure (without fever)?
a. Yes
b. No
c. I don't remember

15. Did you or your partner have a febrile seizure during your own childhood?
a. Yes
b. No
c. I don't remember

16. Do you or your partner have an epilepsy diagnosis?
a. Yes
b. No
c. I don't remember

17. If you have any other children, have they had any febrile seizures?
a. Yes
b. No
c. I don't remember

18. If you have any other children, have they been diagnosed with epilepsy?
a. Yes
b. No
c. I don't remember

19. In yours or wife/husband's family, is there anyone who has been diagnosed with febrile seizure or epilepsy?
a. Yes
b. No
c. I don't remember

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Case Report

Bannayan-Riley-Ruvalcaba Syndrome in a Case Evaluated Due to Multinodular Goiter

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ABSTRACT

Bannayan-Rıley-Ruvalcaba syndrome (BRRS) is characterized by macrocephaly, pigmented macules on the glans penis and benign mesodermal hamartomas. 9.6-year-old boy was referred to the pediatric surgeon following an observation of a subcutaneous lipomatous lesion and numerous nodules in the thyroid gland via ultrasonography performed due to swelling in the neck first noticed approximately 3 months previously. Thyroid ultrasonography revealed numerous nodules with distinct margins in both lobes of the thyroid gland, some exhibiting calcification and others hypoechoic areas, and a total thyroidectomy was performed due to a suspicion of malignity. After surgery, the patient was referred to the Pediatric Endocrinology Department. On physical examination, his weight was 30 kg [standard deviation score (SDS): -0.38], height 140 cm (SDS: 0.71) and head circumference 59.5 cm (SDS: +3.21). Pubic hair was Tanner stage 2, bilateral testes 3+3 mL palpable. There was multiple hyperpigmented lesions on the penile skin. His past medical history revealed that pubic hair development was reported at the age of 8 years. Laboratory examinations revealed a 17-OH progesterone level of 4.8 ng/mL, bone age compatible with 8 years. P. V281L heterozygous mutation was determined via CYP21A2 mutation screening performed for non-classic congenital adrenal hyperplasia. BRRS was primarily suspected in this case of macrocephaly, lipomatous lesions and pigmented macular lesions on the penis. Heterozygous p.C136R mutation was determined via PTEN mutation scanning.
Keywords: Bannayan-Riley-Ruvalcaba syndrome, thyroidnodule, macrocephaly

Introduction

Mutation of the PTEN tumor suppression gene leads to PTEN hamartoma tumor syndrome (PHTS). PHTS includes Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome (BRRS) and Proteus-like syndrome (1,2). BRRS is the pediatric form of PHTS and is characterized by macrocephaly, pigmented macules on the glans penis and benign mesodermal hamartomas (primary subcutaneous and visceral lipomas, multiple hemangiomas and intestinal polyp). These cases may be accompanied by dysmorphic findings, joint hyperelasticity, pectus excavatum, scoliosis, café-au lait spots, frontal bossing, hypertelorism, a short palpebral fissure, a long philtrum and proximal muscle myopathy (3). Growth and mental retardation may be seen in half of these cases. Intestinal polyposis may be seen in 35-40% of cases, and clinical findings of anemia, diarrhea and small intestinal invagination may also be observed (3-5).

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In addition, 30% of cases of BRRS have been shown to be at risk of multinodular goiter, thyroid adenoma, differentiated non-medullary thyroid cancer or Hashimoto's thyroiditis (6).

Case Report

9.6-year-old boy was referred to the Pediatric Surgery Department following an observation of a subcutaneous lipomatous lesion and multiple nodules in the thyroid gland via ultrasonography performed due to swelling in the neck first noticed approximately 3 months previously. Detailed thyroid ultrasonography revealed multiple nodules with distinct margins in both lobes of the thyroid gland, some exhibiting calcification and others hypoechoic areas. Following a total thyroidectomy performed due to a suspicion of malignity, the case was referred to the Pediatric Endocrinology Department. On physical examination, the patient's weight was 30 kg [standard deviation score (SDS): -0.38], height 140 cm (SDS: 0.71) and head circumference 59.5 cm (SDS: +3.21). Axillary hair was not present, pubic hair was Tanner stage-2, testes were 3 mL in size and hyperpigmented lesions on the penile skin were observed (Figure 1). Family history revealed that the patient's maternal grandmother had been diagnosed with colon cancer at the age of 42. Laboratory examinations at the time of presentation revealed free thyroxine: 0.58 ng/dL (0.89-1.76) and thyroid-stimulating hormone: 89.2 mU/L (0.35-5.5). Full blood count, kidney and liver functions and ion levels were within normal limits. 2 mcg/kg/d L-thyroxin for hypothyroidism was started. Investigations were performed for premature pubarche with the findings as follows; follicle stimulating hormone: 0.78 mIU/mL (0.26-3), luteinizing hormone: 0.2 mIU/mL (0.02-0.3) free testosterone: 1.4 pg/mL (0.4-0.9), total testosterone: 0.1 ng/dL (<2.5-10), dehydroepiandrosterone sulfate: 93 mcg/dL (13-83), 17-OH progesterone: 4.8 ng/mL (<0.9) cortisol: 12 mcg/dL (3-21), adrenocorticotropic hormone: 22 pg/mL (6-48) and bone age of 8 years. His 17-OH progesterone level was high, and a p.V281L heterozygous mutation was determined via CYP21A2 mutation scanning performed for non-classic congenital adrenal hyperplasia. Since the patient's bone age was not advanced, we decided to maintain monitoring without treatment. The post-thyroidectomy pathology report was compatible with follicular nodular disease. The case was assessed as BRRS based on the macrocephaly, lipomatous lesions and pigmented macular lesions on the penis. Polypoid structures were observed in the bulbus and throughout the colonic mucosa via endoscopy performed in light of gastrointestinal system lesions, and monitoring was recommended. Cranial magnetic resonance imaging (MRI) in this case with macrocephaly revealed bilateral hamartomatous lesions located in the bilateral cerebral hemisphere anterior periventricular deep white matter, and monitoring with annual cranial MRI was decided upon. Heterozygous p.C136R mutation was determined via PTEN mutation scanning (Figure 2). We report this case in which CYP21A2 mutation was determined incidentally together with PTEN gene mutation due to the coincidence of two different mutations and the rarity of the phenomenon. The inform consent was taken from the patients' parents for publication.

Figure 1. Hyperpigmented lesions on the penis

Discussion

PHTS is an autosomal dominant inherited disease resulting from a germline mutation in the ***PTEN*** gene. BRRS, the pediatric form of PHTS, was first described in 1971 (7). BRRS is characterized by macrocephaly, pigmented macules on the glans penis and benign mesodermal hamartomas (4). No diagnostic criteria for BRRS has been described. Marsh et al. (1) proposed the presence of at least 3 of macrocephaly, lipomatosis, hemangiomas and pigmented macules on the glans penis as diagnostic, while Parisi et al. (8) considered the presence of 2 out of 3 findings described as macrocephaly, hamartomas (lipoma, hemangioma or intestinal polyp) as diagnostic.

Our case was first referred to our clinic by the Pediatric Surgery Department following a total thyroidectomy performed following determination of multinodular goiter, thyroid nodules containing calcification and a hypoechoic area via ultrasonography. The risk of cancer associated with BRRS is still unclear (9). However, differentiated thyroid cancers are thought to derive from follicular adenomas.

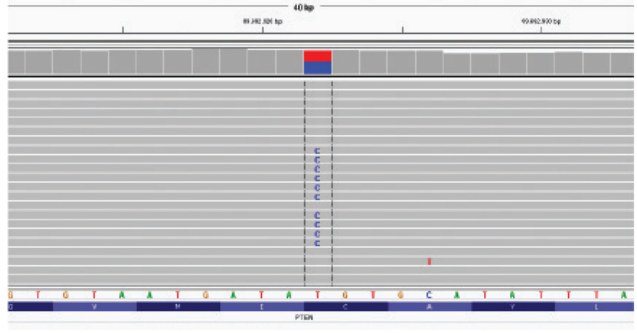

Figure 2. *PTEN* p.C136R (c.406TC)

Prophylactic surgery is preferred in these cases since oxyphilic and follicular cytology cannot clearly differentiate between benign and malign nodules (10-12). However, prophylactic thyroidectomy is not recommended in cases of BRRS without thyroid nodule. Multiple adenomatoid thyroid disease and lymphocytic thyroiditis are frequently seen in cases of BRRS (13). Total thyroidectomy was performed in our case due to suspected malignant nodule via thyroid ultrasonography. The postoperative pathology report was compatible with follicular adenoma.

Several subcutaneous lesions, the largest of which was 2x1.5 cm in size and suggestive of lipoma were observed on the neck and thoracic anterior wall via superficial tissue ultrasonography of the cutaneous lesions. Following dermatological consultation regarding the lesions on the penis determined, under the physical examination, that these were benign penile lentiginous lesions, and annual monitoring of these together with the lipomatous lesions on the body was advised.

Intestinal hamartomatous polyp development has been reported in 35-40% of cases of BRRS (14). A polypoid appearance was also observed along the esophagus, bulbus and the entire colon in our case, and the asymptomatic patient was referred to the Pediatric Gastroenterology Department for observation. It was suggested that the polyps in these cases may be associated with invagination and rectal bleeding, but no evidence has been obtained to show that this increases the risk of colorectal cancer. No fecal occult blood, investigated for screening purposes, was determined in our case.

The cancer screening protocol in patients with BRRS is not explicitly described, although 6 monthly complete blood count, urine tests and thyroid and abdominal ultrasonography are recommended. Monitoring with fecal occult blood investigation and periodic MRI for the risk of intracranial tumor are recommended in cases in which intestinal polyp is determined (15). Hamartomatous lesions in bilateral hemisphere anterior periventricular deep white matter and left parietal deep white matter were observed via cranial MRI in our case. The Oncology and Brain Surgery departments were consulted and monitoring with annual MRI was advised. Neurodevelopmental development with a total IQ 99 score from the WISC-R test administered by a psychologist was evaluated as within normal limits.

BRRS is inherited in an autosomal dominant manner, but a new mutation is determined in 37% of cases. ***PTEN*** gene mutation positivity has been determined in 50-60% of cases with a clinical diagnosis of BRRS (1). PTEN is a tumor suppressor gene located on the long arm of the 10^{th} chromosome. After getting informed consent from the parents, DNA was extracted from peripheral leucocytes using standard methods. Heterozygous p.C136R (TGT>CGT) ***PTEN*** gene mutation, which was previously identified, was also positive in our case. Mutation screening was also performed for the parents and sibling due to autosomal dominant inheritance, but no mutation was determined. Despite a history of colon cancer at the age of 42 in the maternal grandmother, genetic analyses could not be performed since she was no longer alive. PTEN mutation-positive find a genotype/phenotype correlation among 42 patients from 26 families with PTEN mutations and clinical features of BRRC.

In conclusion, other accompanying pathologies can be determined with careful systemic physical examination in patients in whom thyroid nodule is determined. Cases in which BRRS, one of the PHTS, is suspected should be monitored with a multidisciplinary approach including pediatricians, pediatric endocrinologists, gastroenterologists, neurologists, oncologists, dermatologists and pediatric surgeons.

Ethics

Informed Consent: The inform consent was taken from the patients' parents for publication.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.K., S.Ö., A.Ç., Concept: Ö.K., S.Ö., Ş.D., D.G., Design: Ö.K., S.Ö., Ş.D., D.G., Data Collection or Processing: Ö.K., H.O., A.Ç., Y.E., Analysis or Interpretation: Ö.K., S.Ö., H.O., Y.E., Ş.D., Literature Search: Ö.K., S.Ö., Writing: Ö.K., S.Ö.

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References

1. Marsh DJ, Kum JB, Lunetta KL, et al. PTEN mutation spectrum and genotype-phenotype correlations in Bannayane-Riley Ruvalcaba syndrome suggest a single entity with Cowden syndrome. Hum Mol Genet 1999;8:1461-72.
2. Eng C. Will the real Cowden syndrome please stand up: revised diagnostic criteria. J Med Genet 2000;37:828-30.
3. Hendriks YM, Verhallen JT, van der Smagt JJ, et al. Bannayan-Riley-Ruvalcaba syndrome: further delineation of the phenotype and management of PTEN mutation-positive cases. Fam Cancer 2003;2:79-85.
4. Haggitt RC, Reid BJ. Hereditary gastrointestinal polyposis syndromes. Am J Surg Pathol 1986;10:871-7.
5. Harned RK, Buck JL, Sobin LH. The hamartomatous polyposis syndromes: clinical and radiologic features. AJR Am J Roentgenol 1995;164:565-71.
6. Blumenthal GM, Dennis PA. PTEN Hamartoma tumor syndromes. Eur J Hum Genet 2008;16:1289-1300.
7. Bannayan GA. Lipomatosis, angiomatosis, and macrencephalia. A previously undescribed congenital syndrome. Arch Pathol 1971;92:1-5.

8. Parisi MA, Dinulos MB, Leppig KA, Sybert VP, Eng C, Hudgins L. The spectrum and evolution of phenotypic findings in PTEN mutation positive cases of Bannayane Rileye Ruvalcaba syndrome. J Med Genet 2001;38:52-8.
9. Ngeow J, Mester J, Rybicki LA, Ni Y, Milas M, Eng C. Incidence and clinical characteristics of thyroid cancer in prospective series of individuals with Cowden and Cowden-Like syndrome echaracterized by germline PTEN, SDH, or KLLN alterations. Article J Clin Endocrinol Metab 2011;96:2063-71.
10. Corrias A, Mussa A. Thyroid Nodules in Pediatrics: Which ones can be left alone, which ones must be investigated, when and how. J ClinRes Pediatr Endocrinol 2013;5:57-69.
11. Corrias A, Mussa A, Baronio F, et al. Diagnostic features of thyroid nodules in pediatrics. Arch Pediatr Adolesc Med 2010;164:714-9.
12. Corrias A, Cassio A, Weber G, et al. Thyroid nodules and cancer in children and adolescents affected by autoimmune thyroiditis. Arch Pediatr Adolesc Med 2008;162:526-31.
13. Smith JR, Marqusee E, Webb S, et al. Thyroid nodules and cancer in children with PTEN hamartoma tumor syndrome. J Clin Endocrinol Metab 2011;96:34-7.
14. Haggitt RC, Reid BJ. Hereditary gastrointestinal polyposis syndromes. Am J Surg Pathol 1986;10:871-87.
15. Peiretti V, Mussa A, Feyles F, et al. Thyroid Involvement in Two Patients with Bannayan-Riley-Ruvalcaba Syndrome. J Clin Res Pediatr Endocrinol 2013;5:261-5.

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Case Report

Pediatric Bilateral Pheochromocytoma and Experience of Laparoscopic Cortical Sparing Adrenalectomy

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ABSTRACT

Pheochromocytomas are neuroendocrine tumors. In this report, we present a 15-year-old girl who had cerebral palsy and pheochromocytoma. She also had a diagnosis of hyperinsulinemic hypoglycemia in her history. She underwent bilateral laparoscopic cortical sparing adrenalectomy.
We report the experience of laparoscopic bilateral cortical sparing adrenalectomy of a pediatric pheochromocytoma.
Keywords: Pheochromocytoma, laparoscopic surgery, paraganglioma

Introduction

Pheochromocytomas and paragangliomas are neuroendocrine tumors arising from the chromaffin cells. The term pheochromocytoma is used for tumors that occur in the adrenal gland whereas paraganglioma is used for those of extra-adrenal origin (1). The estimated incidence of pediatric pheochromocytomas is 1 in 50.000 (2). Although they can occur as sporadic tumors, a hereditary basis of the disease and identification of a germ line mutation is higher in children compared to adults, reported varying between 30-70%. Von Hippel-Lindau (VHL) disease, multiple endocrine neoplasia (MEN) 2A, 2B and neurofibromatosis (NF) Type I are the most frequently reported syndromes associated with pheochromocytomas. Therefore, genetic testing is imperative for all children who present with pheochromocytoma, regardless of familial history (1,3).

The clinical presentation of childhood pheochromocytoma is highly variable. Symptoms are mostly due to the elevated levels of catecholamines. Sustained hypertension is found in more than 60% of pediatric pheochromocytoma cases. However, the presence of hypertension is not mandatory, and there is no clear correlation between the levels of catecholamines and symptoms (2). Palpitations, headache, excess sweatiness, anxiety and pallor should arouse suspicion of pheochromocytoma in children. Signs and symptoms of sweating, nausea, vomiting, weight loss, polyuria or visual disturbances may also be presenting symptoms in children (2,4).

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Measurement of plasma free metanephrine and normetanephrine or 24-h urinary fractionated metanephrines are considered to be the most accurate biochemical tests for pheochromocytoma (4).

Surgical resection is the treatment of choice and in the setting of bilateral pheochromocytoma, cortical-sparing procedures should be considered (4). Appropriate preoperative medical treatment to block the effects of catecholamines for at least 10-14 days before surgery is mandatory to keep the intraoperative risks minimum. Depending on institutional experience, different protocols have been used to ensure adequate preoperative preparation (1,2,4).

In this article, we report an incidentally diagnosed bilateral pheochromocytoma and aim to highlight the importance of questioning.

Case Report

A 15-year-old motor-mentally retarded girl was admitted to an outpatient clinic for routine check-up of osteopenia. She had been on calcium gluconate and vitamin D therapy for osteopenia secondary to immobilization. Renal ultrasonography was planned to investigate nephrocalcinosis and a 41x34x47 mm mass in the right and 49x25X45 mm mass in the left adrenal gland were identified.

She was born at term after an uneventful pregnancy with a birth weight of 3.200 g. There was a consanguinity between parents. She had a diagnosis of transient hyperinsulinemic hypoglycemia (serum insulin 20 IU/mL, glucose 34 mg/dL) during the neonatal and early infancy period and had been on diazoxide therapy. Her parents had ceased administering the drugs of their own choice. The family history was unremarkable regarding pheochromocytoma and/or adrenal mass or hypertension. After further questioning, her mother complained regarding sweating, anxiety and flushing attacks.

On physical examination, her weight was 45 kg (-1.76 standard deviation score), however, her height was not evaluated properly due to contractures. Her blood pressure was 142/88 (99^{th} percentile/adjusted for age and gender, it was 134/88), her heart rate was 72 beats per minute. She had severe increased muscle tone, rigidity and contractures at multiple joints. Further questioning revealed that the patient had had attacks of flushing and diaphoresis since 1 year of age. Ambulatory blood pressure monitoring revealed hypertension. Twenty-four hour urinary metanephrine was 2.761 µg/day (normal value: 52-341), normetanephrine was 1.198-7.145 µg/day (normal value: 88-444), vanillymandelic acid was 22 mg/day (normal value: 3.3-6.5), serum aldosterone (supine) was 178 pg/mL (n= 20-220), serum renin was 83 pg/mL (n=5.41-34.5), adrenocorticotropic hormone (ACTH) was 40.60 pg/mL (normal: 7.20-63.3 pg/mL), DHEA-SO4 was 28.1µg/dL, total testosterone was 0.28 ng/mL, cortisol was 10.4 µg/dL.

Contrast enhanced abdominal computed tomography (CT) revealed that the density of masses were 14 and 22 Hounsfield units respectively (Figure 1). An iodine^{123} metaiodobenzylguanidine (I^{123}MIBG) scan revealed an increased uptake at the adrenal glands.

Due to hypertensive episodes (121/85-145/88 mmHg) being detected in the preoperative evaluation, the patient was hospitalized and hypertension was stabilized with increasing doses of phenoxybenzamine (final dose: 40 mg/day) under ambulatory blood pressure monitoring 14 days prior to surgery.

On the day of surgery, firstly a laparoscopic transperitoneal partial adrenalectomy was performed for the left adrenal mass (5-6 cm in diameter) with clear borders. Preoperative hypertensive attacks were managed with phenoxybenzamine. In the same session, the patient was re-positioned for the right adrenalectomy and unlike the preoperative CT scan report, 3 other right adrenal masses were detected. Significantly inflammated and stiff masses were resected laparoscopically. Minor bleeding was easily managed with vessel sealing devices. The masses were removed through a laparoscopic endo-bag without complication.

Following bilateral laparoscopic cortical sparing adreneloctomy, the patient remained normotensive. Postoperatively, laboratory examination revealed normal 24-hour urinary metanephrine (22 µg/dL), normetanephrin (538 µg/dL), noradrenalin (90 µg/dL) dopamine (337 µg/dL) and adrenalin (1.9 µg/dL) levels. An I123MIBG scan showed normal uptake. Hydrocortisone treatment, which was started postoperatively, was tapered and then discontinued. Serum cortisol levels were 9.75-2.58 µg/dL, ACTH levels were 96.7-10.3 pg/mL, respectively (08:00 am & 23:00 pm).

The diagnosis of PHEO was confirmed histologically. Genetic analyses of RET, VHL, ABCC8, KCNJ11, HNF4A genes were examined regarding the history of hyperinsulinemic hypoglycemia and no mutation was detected.

During her follow up, twelve months postoperatively, the patient remained normotensive with normal serum cortisol, ACTH levels (11.2 µg/dL and 23 pg/mL) and urinary catecholamine levels. Informed consent was taken from family.

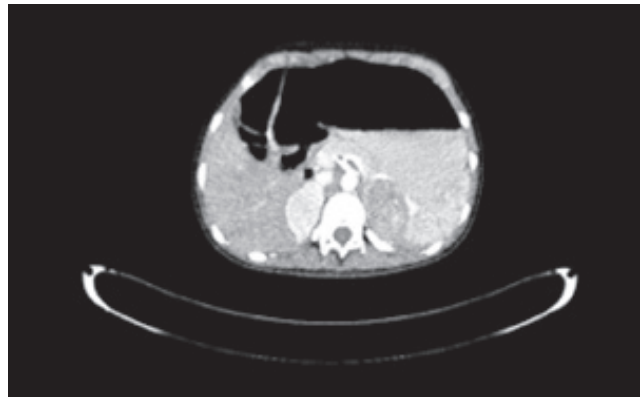

Figure 1. Arterial phase computed tomography of the adrenal masses

Discussion

The clinical presentation of pediatric pheochromocytomas is variable ranging from asymptomatic to sudden death. Sustained hypertension has been reported in 60-95.8% of these patients (2,4-6) The presence of the classical symptom triad (headache, sweating and palpitations) was reported more often in children than adults (4,6). Our case had a typical presentation of the disease, however, regarding her mental retardation; these symptoms (sweating, palpitations and anxiety) were realized belatedly via further questioning.

Measurements of plasma and/or urinary metanephrines, normetanephrines are the most reliable tests for a biochemical diagnosis with almost 100% sensitivity. An elevation of these analyses 4-fold above the reference range is associated with high probability of tumor (2,4-6). Our case had a diagnostic elevation of urinary metanephrines and normetanephrines.

The initial test of choice for tumor location is magnetic resonance imaging or CT which have similar diagnostic sensitivities. For functional testing, I123MIBG scintigraphy is a highly specific test that confirms the catecholamine-secreting nature of the tumors and it can locate tumors not seen with cross-sectional imaging (2).

Approximately 59% of sporadic pheochromocytomas or paragangliomas which are diagnosed in children of <18 years old and up to 70% of those that are diagnosed in children of <10 years old are associated with germline mutations (7). Commonly linked syndromes are VHL, MEN 2A/2B (RET gene), NF1 and paraganglioma syndromes (SDHD, SDHC, SDHB genes). The critical role of VHL gene for □-cell function has been reported before. There have been a few mice studies regarding VHL gene deletion and severe hypoglycemia. These studies reported that deletion of VHL gene in the pancreatic □ cells caused postnatal lethal hypoglycemia. However, the hypoglycemic state was neither due to impaired insulin secretion nor insulin receptor hypersensitivity (8-10). In this respect, we examined VHL and ABCC8, KCNJ11, HNF4A genes in our case, however, no mutation was detected. To the best of our knowledge, pheochromocytoma accompanying transient hyperinsulinemic hypoglycemia has not been reported before. This might be a coincidence, however further genetic analyses such as paraganglioma syndromes are needed before accepting this state as coincidence.

Cortical sparing adrenalectomy is preferred in patients with bilateral disease to avoid life-long glucocorticoid deficiency (2,4,6). Both open and laparoscopic approaches have been employed depending on the surgeon's experience. Our case had an uneventful and successful laparoscopic transperitoneal cortical sparing surgery and post-operative cortisol levels remained normal at follow-up.

As a conclusion, a genetic analysis is suggested in all pediatric pheochromocytomas regardless of family history and cortical sparing adrenalectomy should be the choice of preference in bilateral cases. This minimal invasive technique for cortical sparing surgery is also efficient and safe in these patients.

Ethics

Informed Consent: Consent was taken from family.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and medical Practices: A.A., S.Ö., A.Ç., Z.D., Ş.D., A.Ab., E.B., Concept: A.A., Design: A.A., Data Collection or Processing: A.A., S.Ö., A.Ab., Analysis or Interpretation: A.A., S.Ö., A.Ab., Literarture Search: A.A., Writing: A.A., S.Ö.

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

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References

1. Ein SH, Pullerits J, Creighton R, Balfe JW. Pediatric pheochroocytoma. A 36-year review. Pediatr Surg Int 1997;12:595-8.
2. Waguespack SG, Rich T, Grubbs E, et al. A current review of the etiology, diagnosis and treatment of pediatric pheochromocytoma and paraganglioma. J Clin Endocrinol Metab 2010;95:2023-37.
3. Martins R, Bugalho MJ. Paragangliomas/Pheochromocytomas: Clinically oriented genetic testing. Int J Endocrinol 2014;2014:794187.
4. Havekes B, Romijn JA, Eisenhofer G, Adams K, Pacak K. Update on pediatric pheochromocytoma. Pediatr Nephrol 2009;24:943-50.
5. Choat H, Derrevere K, Knight L, Brown W, Mack EH. SDHB-associated Paraganglioma in a pediatric patient and literature review on hereditary pheochromocytoma-paraganglioma syndromes. Case Rep Endocrinol 2014;2014:502734.
6. Mishra A, Mehrotra PK, Agarwal G, Agarwal A, Mishra SK. Pediatric and adolescent pheochromocytoma: Clinical presentation and outcome of surgery. Indian Pediatr 2014;51:299-302.
7. Neumann HP, Bausch B, McWhinney SR, et al. Germ-line mutations in nonsyndromic pheochromocytoma. N Engl J med 2002;346:1459-66.
8. Puri S, Cano DA, Hebro M. A role for von Hippel-Lindau protein in pancreatic B cell function. Diabetes 2009;58:433-41.
9. Puri S, Garcia_Nunez A, Hebrok M, Cano DA. Elimination of Von Hippel-Lindau function perturbs pancreas endocrine homeostatis in mice. PLoS ONE 2013;8:72213.
10. Kurabayashi A, Kakinuma Y, Morita T, Inoue K, Sato T, Furihata M. Conditional VHL gene deletion causes hypoglycemic death associated with disproportionately increased glucose uptake by hepatocytes through an upregulated IGF-1 receptor. PLoS ONE 2013;8:69139.

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Case Report

Dental Management of Hypophosphatemic Vitamin D Resistant Rickets

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ABSTRACT

Vitamin D-Resistant Rickets (VDRR) is an X-linked disease, causing mineralization disturbances of hard tissues such as bones and deciduous and permanent dentition. The dental findings of VDRR are enlarged pulp horns and chambers, defective enamel/dentin tissue, pulpitis, pulp necrosis, periapical recurrent abscesses and periapical complications without dental caries or trauma. The treatment options of this condition are extraction, endodontic approaches such as pulpotomy/pulpectomy, restorative and preventive applications. The aim of this case report is to summarize the dental clinical, radiographical, histopathological findings and treatment options of VDRR in a 4.5-year-old girl.
Keywords: Vitamin D Resistant Rickets, dentinal clefts, dental abscess, histopathology, primary teeth

Introduction

Vitamin D plays a vital role in the absorption of calcium and phosphate. Low levels of vitamin D can trigger the body to release hormones that lead to the eventual loss of calcium and phosphate from bones, which leads to insufficient bone mineralization. Vitamin D Resistant Rickets (VDRR) is also known as X-linked hypophosphatemia with a prevalence of 1:20.000 people (1-4). It is characterized by a calcium and phosphate metabolism disorder affecting mineralized tissues, bone and teeth (1,5). VDRR was first documented by Albright et al. (6) (1937) and mineralization defects of hard tissues in these cases are derived from renal transepithelial transport disturbance resulting in decreased tubular reabsorption of phosphate and hypophosphatemia (1,4,7). Physical findings are growth failure, bowing of the legs, short stature and walking disturbances (4,7,8).

VDRR has been connected with several primary and permanent teeth alterations. Dental findings of this condition are enlarged pulp chambers, pulp horns which spread outside the dentino-enamel junction, enamel and dentine defects, poorly defined lamina-dura, short roots and hypoplastic alveolar ridge (4,9-11).

Histological analysis point to clefts in dental hard tissues especially dentine, marked globular dentine and increased predentin width (2,7,9). The combination of all these factors contribute to recurrent dental abscesses in VDRR cases. Bacteria and their toxins which come from the oral cavity to the pulp cause pulpitis, pulp necrosis, periapical recurrent abscess or periapical complications without dental caries (1,2,4,5,7,9-14).

In VDRR cases, in spite of the impairment of dentine mineralization, it is known that the odontoblastic cell function is normal (15,16). Additionally, dentine tissue is more

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affected than enamel (4). Furthermore, because enamel and dentine formation occur between 4 months in-utero and 11 months of age, deciduous teeth defects cannot be avoided. However, permanent dentition development can be improved by medical therapy after birth. Therefore, mineralized tissue defects are more common in primary dentition than permanent dentition (3,4,16).

This case report aims to present dental clinical, radiographic and histological features of a VDRR case at our clinic.

Case Report

A 4.5-year-old female patient was referred to our clinic with the complaint of a speech problem, including delayed speech and difficulty in making some sounds. As a result of questioning her medical history, it was discovered that she had VDRR and its physical findings (Figure 1).

Clinical dental examination revealed that there was fistula formation at the periapical area of the left maxillary primary central incisor without caries and a dental trauma history (Figure 2) and, as a result of radiographic examination, that a related tooth also had a periapical lesion (Figure 3). Additionally, the right maxillary primary central incisor had colour changes but a cold vitality test showed a positive response. Furthermore, caries of mandibular primary first molars were diagnosed both clinically and radiologically. In addition, during speech examination, problems with the 'z/s' sounds were noted and consultation with the orthodontics department showed that the patient had a "deep palatal vault".

The parents of the patient were informed about the treatment and their consent was obtained. Initially, the left maxillary primary central incisor was extracted and the mandibular first primary molars were restored with compomer (Dyract XP, Dentsply, DeTrey GmbH). After that, to avoid infantile swallowing, improve speech ability and for aesthetic purposes, a removable partial child prosthesis was applied (Figure 4). Histological evaluation was carried out in order to diagnose dental manifestation of VDRR accurately. In the histological assessment, a healthy primary incisor tooth which exfoliated physiologically was used to compare with the patient's left upper primary central incisor.

After fixing the dental tissues of the extracted teeth with 10% buffered formalin, they were decalcified with 8% formic

Figure 1. The patient with Vitamin D Resistant Rickets; a) facial view, b) physical findings

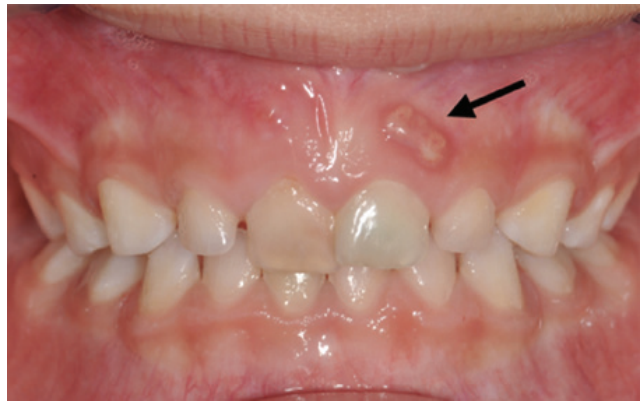

Figure 2. Intraoral view of the patient and fistula formation (arrow)

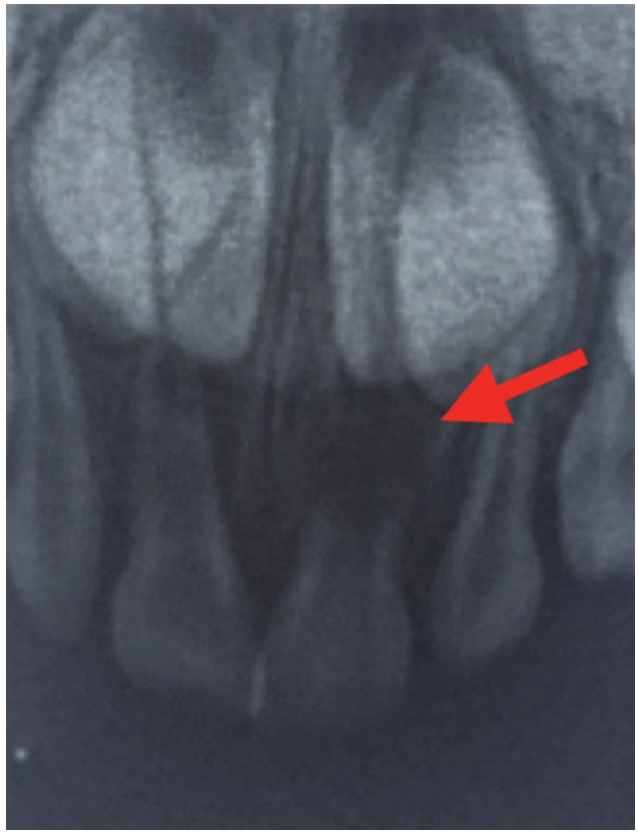

Figure 3. Periapical radiograph of the primary incisors and the radiolucency around the periapical region of tooth 61 (arrow)

acid / 8% hydrochloric acid. Following the routine histological preparations, the teeth were embedded paraffin sectioned to obtain sections 4 µm in thickness. These sections were stained using hematoxylin-eosin and examined under a light microscope (Zeiss AxioScope A1, Carl Zeiss, Germany).

Histological assessment of the teeth showed that, although the odontoblastic cell layer was intact, the predentin layer width was increased when compared with a healthy primary incisor tooth (Figure 5). Additionally, the evaluation revealed that the specimens had increased predentin, marked globular dentine with hipomineralized areas, dentinal clefts and dilated dentinal tubules (Figures 6,7).

Finally, in order to provide oral health care, oral hygiene procedures were given to the patient and her parents. Topical fluoride varnish (Duraphat, Colgate-Palmolive, GmbH, Hamburg, Germany) was applied to all the teeth to avoid probable pulp pathologies and the patient had follow-ups periodically.

Discussion

VDRR is a disease which is characterized by defective reabsorption of phosphate from the proximal renal tubule

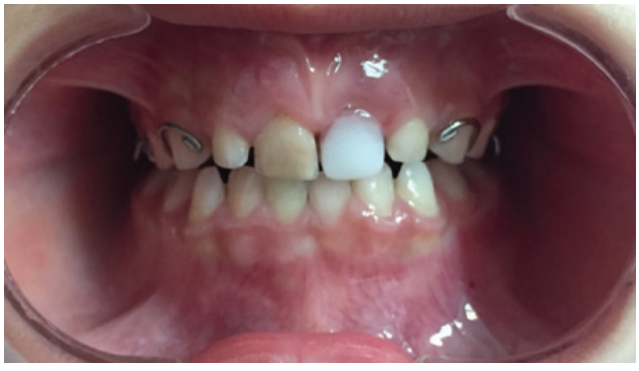

Figure 4. Removable partial child prosthesis

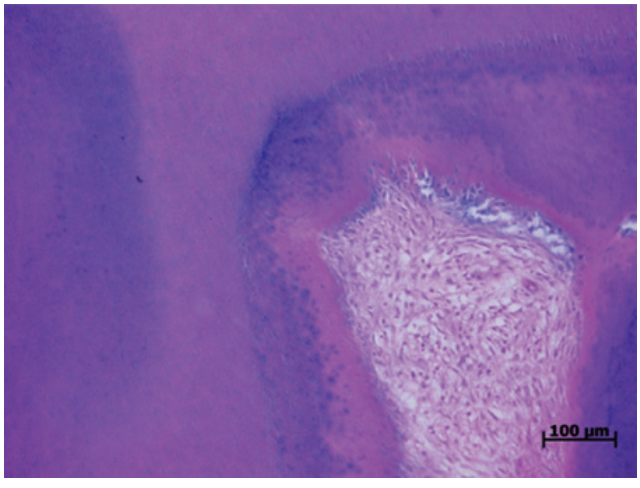

Figure 5. Histological section of healthy primary incisor as a control tooth

(1,7,9). Hypophosphatemic VDRR may be less severe when it occurs in the late stages of life and does not cause bone deformity. In a study of the orthodontic treatment of a 9-year-old girl with VDRR, Kawakami and Takano-Yamamoto (17) (1997) reported that VDRR can be diagnosed by dental examination.

In this VDRR case, histological examination of the extracted tooth showed dentinal clefts/dilated dentinal tubules and these conditions agreed with the dental findings of VDRR. Furthermore, as noted in some cases (1,7,9), marked globular dentine, increased predentin width and intact odontoblastic cell layer were seen in the present case. The enamel in these cases was reported to be normal but thinner contrary to defective dentin tissue (4,11). However, sometimes, enamel cracks (18,19) and enamel hypoplasia (3,18,20) can be observed in patients.

Prophylactic pulp/endodontic treatments, conservative treatment and tooth extraction may be applied in these cases

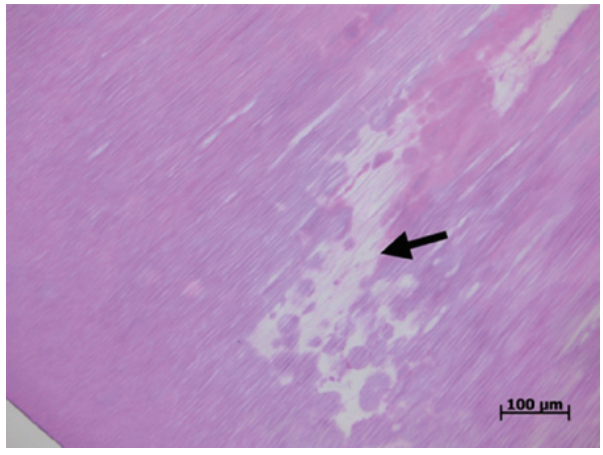

Figure 6. Histological section of the extracted tooth. Note the dentinal clefts and dilated dentin tubules (arrow) (x20 magnification)

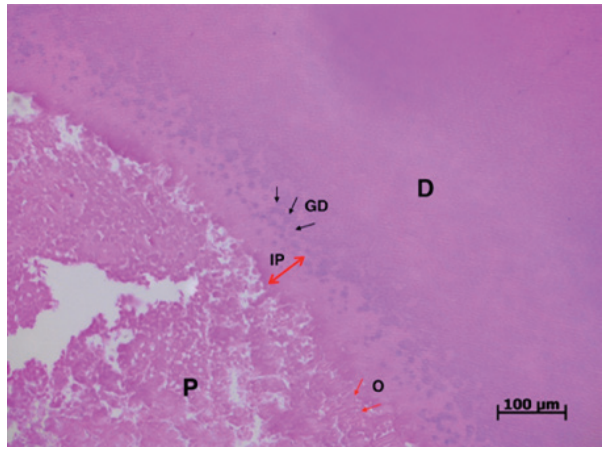

Figure 7. Histological section of the extracted tooth. Note the increased predentin width (IP-red arrow), intact odontoblasts (O - red arrows), globular marked globular dentine (GD - black arrows), P: Pulp, D: Dentine (x20 magnification)

(4,5,21). Although the prophylactic pulpotomy is one of the treatment options of VDRR cases, it is not recommended due to lack of sufficient evidence for a good prognosis (21). In this case, tooth #61 was extracted because of a fistula formation and periradicular lesion. Following extraction, dentin caries were restored and removable denture was applied to avoid infantile swallowing, physiological and speech problems (22). Additionally, dentin caries of the mandibular first primary molars were restored with polyacid-modified composite resin (compomer) to prevent probable pulpal disease.

In addition to progressive caries and abscess formation, attrition of the dental mineralized tissues is also seen in VDRR cases (9). In these cases, to avoid attrition and microfractures of enamel and dentine, prefabricated metal or polycarbonate resin crowns can be applied (23). However, in the present case, this application was not carried out because there was no defect in the enamel and the perforation risk to the pulp chambers (16). Finally, following the therapeutic, restorative and preventive applications, the patient was recalled for periodical check-ups of the prosthetic appliance, general dental condition, orthodontic examination and caries preventing procedures.

Ethics

Informed Consent: Consent form was filled out by the parents of the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.D., A.T.A., E.E., F.T.Ö., Concept: A.D., F.T.Ö., Design: A.D., F.T.Ö., Data Collection or Processing: A.D., A.T.A., Analysis or Interpretation: A.D., F.T.Ö., Literature Search: A.D., A.T.A., E.E., F.T.Ö., Writing: A.D., A.T.A.

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References

1. Pereira CM, Andrade CR, Vargas PA, Coletta RD, de Almeida OP, Lopes MA. Dental alterations associated with X-linked hypophosphatemic rickets. J Endod 2004;30:241-5.
2. Batra P, Tejani Z, Mars M. X-linked hypophosphatemia: dental and histologic findings. J Can Dent Assoc 2006;72:69-72.
3. Souza MA, Soares Junior LA, Santos MA, Vaisbich MH. Dental abnormalities and oral health in patients with hypophosphatemic rickets. Clinics (Sao Paulo) 2010;65:1023-6.
4. Souza AP, Kobayashi TY, Lourenço Neto N, Silva SM, Machado MA, Oliveira TM. Dental manifestations of patient with Vitamin D-resistant rickets. J Appl Oral Sci 2013;21:601-6.
5. Hernandez GG, Laguna FB. Dental characteristics of hypophospathemic rickets. Case report. Revista Odontológica Mexicana 2013;17:101-8.
6. Albright F, Butler AM, Bloomberg E. Rickets resistant to vitamin D therapy. Am J Dis Child 1937;54:529-47.
7. Tümen EC, Yavuz I, Suer Tümen D, Atakul F. Dental and histologic findings of X-linked hypophosphatemic vitamin D-resistant rickets: A case report. International Dental and Medical Disorders 2008;1:37-42.
8. Zambrano M, Nikitakis NG, Sanchez-Quevedo MC, Sauk JJ, Sedano H, Rivera H. Oral and dental manifestations of vitamin D-dependent rickets type I: report of a pediatric case. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2003;95:705-9.
9. Murayama T, Iwatsubo R, Akiyama S, Amano A, Morisaki I. Familial hypophosphatemic vitamin D-resistant rickets: dental findings and histology study of teeth. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2000;90:310-6.
10. Cremonesi I, Nucci C, D'Alessandro G, Alkhamis N, Marchionni S, Piana G. X-linked hypophosphatemic rickets: Enamel abnormalities and oral clinical findings. Scanning 2014;36:456-61.
11. S Sarat G, Priyanka N, Prabhat MP, Raja Lakshmi C, Bhavana SM, Ayesha Thabusum D. Hypophosphatemic Rickets in Siblings: A Rare Case Report. Case Rep Dent 2016;2016:4803167.
12. Seow WK. Diagnosis and management of unusual dental abscesses in children. Aust Dent J 2003;48:156-68.
13. Goodman JR, Gelbier MJ, Bennett JH, Winter GB. Dental problems associated with hypophosphataemic Vitamin D resistant rickets. Int J Paediatr Dent 1998;8:19-28.
14. Andersen MG, Beck-Nielsen SS, Haubek D, Hintze H, Gjørup H, Poulsen S. Periapical and endodontic status of permanent teeth in patients with hypophosphatemic rickets. J Oral Rehabil 2012;39:144-50.
15. Abe K, Ooshima T, Tong SML, Yasufuku Y, Sobue S. Structural deformities of deciduous teeth in patients with hypophosphatemic vitamin D-resistant rickets. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1988;65:191-8.
16. Tümen EC, Yavuz I, Atakul F. Types of rickets, dental and histologic findings: Review of the literature. Pesq Bras Odontoped Clin Integr 2009;9:241-6.
17. Kawakami M, Takano-Yamamoto T. Orthodontic treatment of a patient with hypophosphatemic vitamin D-resistant rickets. ASDC J Dent Child 1997;64:395-9.
18. Baroncelli GI, Angiolini M, Ninni E, Galli V Saggese R, Giuca MR. Prevalence and pathogenesis of dental and periodontal lesions in children with X linked hypophatemic rickets. Eur J Paediatr Dent 2006;7:61-6.
19. Linglart A, Biosse-Duplan M, Briot K, et al. Therapeutic management of hypophosphatemic rickets from infancy to adulthood. Endocr Connect 2014;14:13-30.
20. Davit-Béal T, Gabay J, Antoniolli P, Masle-Farquhar J, Wolikow M. Dental complications of rickets in early childhood: Case report on 2 young girls. Pediatrics 2014;133:1077-81.
21. Shroff DV, McWhorter AG, Seale NS. Evaluation of aggressive pulp therapy in a population of vitamin D-resistant rickets patients: a follow up of 4 cases. Pediatr Dent 2002;24:347-9.
22. Dominguez A, Aznar T. Removable prostheses for preschool children: report of two cases. Quintessence Int 2004;35:397-400.
23. Yasufuku Y, Kohno N, Tsutsumi N, Ooshima T, Sobue S, Murakami Y, Ikari H. Dental management of familial hypophosphatemic vitamin D-resistant rickets: report of case. ASDC J Dent Child 1983;50:300-4.

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Case Report

Neutropenic Fever in a Two-and-a-Half Month Old Girl: Severe Congenital Neutropenia

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ABSTRACT

Severe congenital neutropenia is a hereditary disease characterized by a low number of neutrophils occurring from the first months of life leading to severe infections. It is rare but threatens life because of severe infections. For this reason, early diagnosis and treatment of this disease is important. Here, we present a case of a two and a half month old girl who was admitted to our clinic with fever and absolute neutropenia was determined in her clinical course.
Keywords: Congenital neutropenia, ELA-2, G-CSF

Introduction

Congenital neutropenia is a disease that develops in bone marrow due to the arrest in promyelocyte or myelocyte maturation and differentiation (1). From the first month of life, clinical manifestations of *staphylococcal, streptococcal, pseudomonas* and fungal infections such as omphalitis, otitis media, pneumonia, abscess have been reported (1,2). The peripheral blood neutrophil count is less than 500/mm^3 (2). Eosinophilia, monocytosis, mild anemia and thrombocytosis may also appear in this disease.

The disease was originally described by Kostmann in 1956. The rate is approximately 1 or 2 in one million, equally prevalent in both male and female (1,2). It usually shows an autosomal recessive transition. It may be either an autosomal dominant transition or sporadic transition. (2). At the molecular level, neutrophil elastase (ELA-2), HAX-1 (HS1-related protein X-1), glucose-6-phosphatase catalytic subunit 3 (G6PC3), growth factor independent 1 - Wiskott-Aldrich syndrome protein) gene defects have been associated with this disease (1).

Granulocyte colony stimulating factor (G-CSF) is used in the treatment and most cases respond to treatment (3). Untreated patients may be lost early due to severe bacterial infections. Since the beginning of G-CSF usage as a treatment, the average life span has significantly increased. However, in these cases undergoing treatment, there is a risk of secondary myelodysplastic syndrome (MDS) and/or acute myeloid leukemia (AML) in the disease course (4). If patients are not lost from infections, cytogenetic changes can occur such as G-CSF receptor mutations in 12% and monosomy 7 in 50%. In the instances of cytogenetic changes, the risk of MDS and AML conversion increases. If these is no response to G-CSF, then stem cell transplantation is performed (1).

Severe congenital neutropenia is encountered quite rarely and mortality is high because of recurrent severe bacterial

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infections in the early stages of life. Genetic analysis is very important in its diagnosis and differential diagnosis. Severe congenital neutropenia should be kept in mind for children who have severe infections in the early stages of their life and blood counts should be carefully examined.

Case Report

A two and a half month old girl was brought in with a fever which had started the previous day and was measured the highest point at 40.1 °C. In her past history, she had been examined by a doctor due to complaints of redness and swelling of the left side of her neck on the 9th day after birth. It was learned that these findings were assessed as a neck abscess and intravenous antibiotic treatment was administered. There was no history of consanguineous marriage or familial disease. On physical examination, the overall situation was good, the patient was conscious and her activity was normal. A systemic examination was normal. Laboratory values included leukocyte count of 6.700/µL, absolute neutrophil count of 100/µL, hemoglobin at 9.2 g/dL, a platelet count of 330.000/µL, mean corpuscular volume as 85fL, mean corpuscular hemoglobin at 28 pcg. Peripheral blood smear showed that erythrocytes were normochromic and normocytic, 86% lymphocytes, 10% monocytes, 4% eosinophils, with no neutrophils and no atypical cells. C-reactive protein was 2.1 mg/dL, procalcitonin was 0.2 ng/mL. Liver and kidney function tests, electrolytes and urine examination were within normal limits. Urine and blood cultures were taken. Because of fever and severe neutropenia, empirical intravenous ampicillin and cefotaxime was started. On the third day, the control count of blood cells showed leukocyte as 4.700/µL with absolute neutrophil 0/µL, hemoglobin 9.2 g/dL, platelet 306.000/µL. In the peripheral smear; no neutrophil or atypical cells were observed, erythrocytes were normochromic and normocytic, monocytes were relatively increased. During the previous hospitalization due to the neck abscess in neonatal period, neutrophil counts were <500/µL. With these findings, congenital neutropenia was considered primarily in this case and a bone marrow aspiration was performed. In the bone marrow examination; cellularity was normal. Promyelocyte, myelocyte, metamyelocyte, band and mature neutrophil forms were absent. There was a relative increase in eosinophils and monocytes. Megakaryocytes were normal in number and morphologically. Erythroid series was also normal and depot cell and haemophagocytosis were not observed (Figure 1). Twenty-four and 72 hour cell culture were also performed from the bone marrow. This was not induced by phytohemagglutinin and evaluated malignant cells, which are usually spontaneous mitosis. Sequence analysis including all exon and exon-intron junction regions of *ELANE / ELA-2*, *HAX1* and *WAS* gene for congenital neutropenia

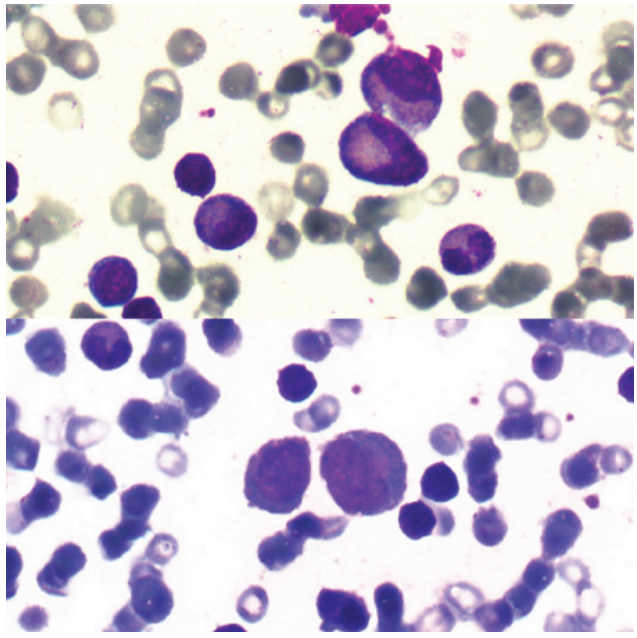

Figure 1. In bone marrow smear; promyelocyte, myelocyte, metamyelocyte, band and mature neutrophil forms were absent

was also performed by DNA isolation from the patient's peripheral venous blood. Bone marrow chromosome analysis revealed normal constitutive karyotype (46, XX). In the genetic analysis, a heterozygous p.A57V (c.170C>T) missense amino acid mutation was observed in the second exon in the *ELANE / ELA-2* gene; No mutations were found in the *HAX1* and *WAS* genes. G-CSF therapy was started due to severe congenital neutropenia. After one week, the neutrophil count was determined as 2000/µL. Consent form was filled out by participant.

Discussion

Severe congenital neutropenia often manifests with clinical manifestations of omphalitis, abscess formation, otitis media, gingivitis and pneumonia within the first six months after birth (1,2,4). Our patient was diagnosed with a neck abscess in the newborn period and there was severe neutropenia in her blood counts. Since there was an abnormal number of neutrophils from birth, severe congenital neutropenia was considered primarily and acquired neutropenic cases and cyclic neutropenia were excluded. Despite the treatment of the infection, neutropenia did not improve and infection-associated neutropenia was not considered primarily. Shwachman-Diamond syndrome was not considered for reasons such as no growth retardation, lack of skeletal anomalies and neutropenia occurring early in life. Other rare diseases which can lead to persistent severe neutropenia including hemophagocytic syndrome, reticular dysgenesis and dyskeratosis congenita were discounted after an analysis of the bone marrow aspiration findings.

ELANE / ELA-2 mutations are the first identified genetic defects in autosomal dominant and sporadic severe congenital neutropenia and cyclic neutropenia (5,6). Approximately 52 different ELANE / ELA-2 mutations have been reported to date (7,8). Neutrophil elastase gene (ELANE / ELA-2) mutation is thought to result in a premature endoplasmic reticulum accumulation of unstructured protein in the cell due to increased stress and premature apoptosis in neutrophil precursor cells, thereby suppressing myelopoiesis (5). In our case, the heterozygous p.A57V (c.170C>T) missense amino acid mutation of the *ELANE / ELA-2* gene was seen in the second exon. This mutation is a nucleotide C nucleotide T replacement according to the ENSEMBL ENST00000263621 transcript and has been reported in the Human Gene Mutation Database under code CM094946. This mutation makes a difference in the amino acid sequence and causes a change in protein production.

No mutations were identified in HAX-1, WAS or G6PC3 genes, which are other mutations associated with severe congenital neutropenia.

In cases of severe congenital neutropenia, although sepsis-related mortality has decreased with the availability of appropriate antibiotics and regular G-SCF therapy in infections, the incidence of MDS or AML development in a 10-year follow-up period has been reported to be 20%. The risk of leukemia transformation is related to the myeloid arrest level in bone marrow, the type of ELANE mutation (C214R, C151Y), the presence of pancytopenia and G-CSF administration. This risk increases if the average dose in G-CSF injection is ≥10 µg/kg/day, the cumulative dose is >10.000 µg/kg and given over a period of more than 10 years. The risk of MDS/AML appears to be around 2.3% per year after 10 years on G-CSF. (9) In our case, G-CSF was administered at 3 µg/kg/day.

In conclusion, severe congenital neutropenia is a rare disease group that causes early death due to severe infections. Mutation analysis and genetic counseling are important for early diagnosis, treatment and prevention because of hereditary transition.

Ethics

Informed Consent: Consent form was filled out by participant.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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References

1. Barış S, Karakoç Aydıner E, Kıykım A, et al. The phenotype-genotype relationship in severe congenital neutropenia patients. Turk Pediatri Ars 2012;47:272-7.
2. Celkan T, Koç BŞ. Approach to the patient with neutropenia in childhood. Turk Pediatri Ars 2015;50:136-44.
3. Welte K, Zeidler C, Dale DC. Severe congenital neutropenia. Semin Hematol 2006;43:189-95.
4. Edeer Karaca N, Aksu G, Gulez N, et al. Clinical, Laboratory and Molecular Approach to Ten Children with Congenital Neutropenia. J Pediat Res 2016;3:7-12.
5. Boztug K, Klein C. Genetic etiologies of severe congenital neutropenia. Curr Opin Pediatr 2011;23:21-6.
6. Dale DC, Person RE, Bolyard AA, et al. Mutations in the gene encoding neutrophil elastase in congenital and cyclic neutropenia. Blood 2000;96:2317-22.
7. Horwitz MS, Duan Z, Korkmaz B, Lee HH, Mealiffe ME, Salipante SJ. Neutrophil elastase in cyclic and severe congenital neutropenia. Blood 2007;109:1817-24.
8. Smith BN, Ancliff PJ, Pizzey A, Khwaja A, Linch DC, Gale RE. Homozygous HAX1 mutations in severe congenital neutropenia patients with sporadic disease: A novel mutation in two unrelated British kindreds. Br J Haematol 2009;144:762-70.
9. Rosenberg PS, Zeidler C, Bolyard AA, et al. Stable long-term risk of leukemia in patients with severe congenital neutropenia maintained on G-CSF therapy. Br J Haematol 2010;150:196-9.

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Case Report

Anaphylaxis in a Newborn Due to Ampicillin

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ABSTRACT

Anaphylaxis, an allergic reaction that is rapid in onset, is rare in the neonatal period due to immaturity of the immunological system. A case of three-day-old male neonate with ampicillin-induced anaphylaxis is reported here. Although drug allergies are rare in newborns, due to their life-threaten features, close monitoring is important.

Keywords: Adverse effect, ampicillin, anaphylaxis, newborn

Introduction

Anaphylaxis is a serious allergic reaction that is rapid in onset and life threatening. After contact with an allergen, mast cells and basophiles release chemical mediators. Increased immunoglobulin E (IgE) is responsible for pathogenesis. The most common causes of anaphylaxis in children are food and medicines. Anaphylaxis caused by drugs are mostly seen in hospitals. Hypersensitivity reactions are common in childhood but they are rare in the neonatal period due to the immaturity of the immunological system (1).

We present this case, due to the ampicillin, which is a commonly used antibiotic in newborn intensive care units, and because of the rare occurrence of anaphylaxis in the newborn period. We would like to emphasize the importance of monitoring patients who are followed up in newborn intensive care units, have an immature immunologic system with respect to life-threatening drug allergies in order to take precautions and determine the treatment approach more effectively.

Case Report

A male infant was born by caesarean section at 36 weeks gestation with a birth weight of 3.235 g. The mother was 36 years old. At birth, the male infant was tachypneic and had retractions, with an Apgar score of five at 1st, and seven at 5th minute after birth. He was hospitalized with a diagnosis of respiratory distress syndrome, intubated and surfactant was given. Since congenital pneumonia could not be distinguished, treatment with ampicillin (50 mg/kg/per dose with 12-hour intervals) and amikasin (15 mg/kg/per dose with 24-hour intervals) was initiated. In his laboratory tests, the following data were obtained: hemoglobin: 17.7 g/dL, leukocyte: 18.130 µL (neutrophil: 7200/µL, lymphocyte: 8030/µL, eosinophil: 1240/µL, monocyte: 1440/µL, basophil: 220/µL), C-reactive protein (CRP): 0.13 mg/L. Echocardiography revealed a patent foramen ovale. Extubated at the 24th hour of his life and continued under observation in room air. There were no pathological indicators in his prenatal history. Paracetamol allergy was present in his father. On the third day of follow-up, ten minutes after the 50 mg/

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kg ampicillin within 15 minutes by intravenous slow push without the extravasation (Penbisin® 500 mg vial, İ.E.Ulagay, İstanbul, Turkey) whole body hyperemia, cyanosis of the extremities, edema of the eyelids-back of the hands and feet, subcostal retraction and stridor evolved (Figure 1). His vital signs were as follows, heart rate: 180/per minute, SpO_2 98%, respiration rate: 70/per minute, blood pressure: 80/60 (65) mmHg, body temperature: 36 °C. The sudden onset fulminant clinical condition was observed as a drug allergy and 2 mg/kg intravenous pheniramine maleate was used due to accessibility as the H1 antagonist at that time. In blood gas parameters, mild metabolic acidosis was detected (pH: 7.26, pCO_2: 41 mmHg, pO_2: 50 mmHg, HCO_3: 18 mEq/L, BE: -8, lactate: 3.4 mmol/L). During the 5th minute of intravenous antihistamine treatment, respiratory distress and skin findings disappeared. Control whole blood count; hemoglobin: 18.3 g/dL, leukocyte: 14.390/µL (neutrophil: 5740/µL, lymphocyte: 5750/µL, eosinophil: 1380/µL, monocyte: 1390/µL, basophil: 130/µL), CRP: 4.6 mg/L were detected. Complete urinalysis, a liver and kidney function test results were observed within the normal limits. There was no evidence of blood culture. Ampicillin therapy was discontinued and the follow-up was continued. Ampicillin specific IgE: <0.1 kU/L (normal value: <0.35 kU/L), serum tryptase value was detected at 7.1 ug/L (normal value <11.4 ug/L). The patient, who had no biphasic reaction, was discharged on the 7th day of life. The verbal consent was taken from the patient's parents.

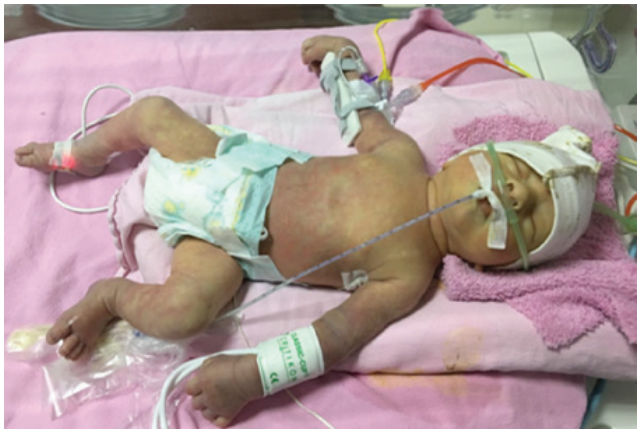

Figure 1. Hyperemia and cyanosis of the extremities with edema of the eyelids-back of the hands developed after ampicillin administration

Discussion

Anaphylaxis is a skin, respiratory, cardiovascular, gastrointestinal symptoms and signs of a hypersensitivity reaction and this reaction can be fatal. The immune system becomes susceptible to an allergen previously encountered. In the event of a recurrence, the clinical signs are revealed by the release of inflammatory mediators by mast cells (1). The diagnosis of anaphylaxis is made by the appearance of signs and symptoms after the allergen encounter incident. Clinical findings such as flashing, generalized edema, dyspnea, bronchospasm, or hypotension are seen during the following minutes or hours. Mediators released from mast cells and basophils cause clinical signs with vasodilatation, increased capillary permeability and platelet aggregation (2). Diagnosis is based on clinical symptoms and findings rather than laboratory findings (1). Mast cells and basophiles may also be activated by IgE-independent mechanisms and may cause "anaphylactoid" reactions with similar clinical features. Anaphylaxis with IgE-mediated immunity or non-immunization mechanisms is less common due to the immaturity of the immunological system during the neonatal period (3). For this reason, the diagnosis of anaphylaxis in the newborn is controversial and it is necessary to evaluate the differential diagnosis in detail. Neonatal sepsis and septic shock, which have clinical findings such as tachycardia, tachypnea and circulatory disturbances, as in our patient, are the first diagnosis that should be considered. Foreign body aspiration, respiratory and gastrointestinal malformations and sudden infant death syndrome should be considered in the differential diagnosis. In our patient, the acute phase reactants were negative (the cut off value of CRP is 5 mg/dL), immature/total neutrophil ratio in peripheral smear <0.2, good general condition and also clinical manifestations began after drug injection so we excluded a sepsis diagnosis. Hereditary angioedema has similar clinical findings to anaphylaxis but no response to adrenaline, antihistamines or steroids and there is also a family history (4). In our patient, there is no history to suggest hereditary angioedema in his family except a paracetamol allergy in his father. Also, the clinical manifestations began after ampicillin therapy, and there was a response to antihistamines. Therefore, a hereditary angioedema diagnosis was excluded.

The number of cases of anaphylaxis during the newborn period in the literature is few. After an intake of cefotaxime, ceftriaxone, ceftazidime, amikacin, cow milk proteins or hepatitis B immunoglobulin, anaphylaxia cases have been reported (1,4-8).

Ampicillin is an aminopenicillin group beta-lactam antibiotic effective against gram positive, gram negative and anaerobic microorganisms which is also commonly used in early sepsis treatment. Anaphylaxis due to penicillin-derived antibiotics is estimated to range from 1% to 10% worldwide, with a life-threatening anaphylaxis rate of 0.02% to 0.05% for all age groups (9).

Anaphylaxis is a condition requiring emergency treatment; oxygen support, monitorization, intravenous fluid therapy, adrenaline, antihistamine and steroid treatment are to be applied (1). Adrenaline (1/1000) is administered intramuscularly at a dose of 0.01 mg/kg. Antihistamine and steroid treatment can be added. It is also seen in the literature

that symptoms are corrected with antihistamine and dexamethasone only in the anaphylactic shock treatment in the newborn (8). In our case, clinical response was seen in five minutes with antihistamine only. No additional medication was needed as the clinical findings of the patient improved.

Approximately 6% of cases with anaphylaxis can recur after 1.3-28.4 hours of recovery (biphasic or recurrent anaphylaxis). Especially with serious anaphylactic cases, recurrences occur more frequently. Also, it should be kept in mind that a delay in adrenaline administration may facilitate this situation (10). There was no biphasic reaction during the 72-hour follow-up in our case.

Also, clinicians should always be reminded of the need to be cautious due to the possible mortal effects of intravenous ampicillin therapy commonly used in routine clinical practice.

Ethics

Informed Consent: The verbal consent was taken from the patient's parents.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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

References

1. Simons FE. Anaphylaxis: Recent advances in assessment and treatment. J Allergy Clin Immunol 2009;124:625-36.
2. Topal E, Bakirtas A, Yilmaz O, et al. Severe anaphylaxis in children: a single-center experience. Pediatr Neonatol 2014;55:320-2.
3. Rupa P, Hamilton K, Cirinna M, Wilkie BN. A neonatal swine model of allergy induced by the major food allergen chicken ovomucoid (Gal d 1). Int Arch Allergy Immunol 2008;146:11-8.
4. Kendigelen P; BaktirClinic Of Anesthesiology And Reanimation Afşin State Hospital Afşin Kahramanmaraş Tureky M, Sucu A, Kaya G. Anaphylaxis after administration of amikacin containing sodium metabisulfite in a premature newborn. Arch Argent Pediatr 2016;114:195-8.
5. Babu TA, Sharmila V. Cefotaxime-induced near-fatal anaphylaxis in a neonate: A case report and review of literature. Indian J Pharmacol 2011;43:611-2.
6. Baumgartner-Bonnevay C, Choquet-Kastylevsky G, Putet G, Bleyzac N, Vial T, Descotes J. Anaphylactic shock associated with ceftriaxone therapy in a newborn. Arch Pediatr 2002;9:1050-2.
7. Soyer OU, Ozen C, Tiras U, Dallar Y. Anaphylaxis in a neonate caused by ceftazidime. Allergy 2010;65:1486-7.
8. Bulbul A, Karadag A, Köklü E, Pamuk U, Sarici SU. Anaphylactic shock due to hepatitis B immunoglobulin in a newborn. J Matern Fetal Neonatal Med 2010;23:1257-9.
9. Cetinkaya S, Tengir T. Penicillin Allergy and Penicillin Allergy Test: Review. J Pediatr 2008;17:175-82.
10. Lee JM, Greenes DS. Biphasic anaphylactic reactions in pediatrics. Pediatrics 2000;106:762-6.

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Case Report

Stenotrophomonas Maltophilia/S. Maltophilia Sepsis Presenting with Perianal Cellulitis and Pneumonia in a Leukemic Child

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ABSTRACT

Infections caused by *Stenotrophomonas maltophilia* may be fatal in diseases such as leukaemia which causes immunodeficiency. Herein, we report a rare case of 8-year-old girl with acute lymphoblastic leukaemia, who developed perianal cellulitis and pneumonia secondary to *S. maltophilia* bacteraemia while undergoing broad spectrum antimicrobial agents for neutropenic fever.
Keywords: *S. maltophilia*, cellulitis, pneumonia, leukaemia

Introduction

Stenotrophomonas maltophilia infections are increasingly seen in immunocompromised patients, as it is an opportunistic pathogen with low virulence (1). Risk factors for *S. maltophilia* infection include prolonged hospitalization in intensive care units, medical devices, use of broad-spectrum antibiotics and malignancy (1,2). Infections are more prevalent during severe neutropenic periods, and in cases in which immunosuppression develops; however, its mode of transmission is not clear. It is thought to invade from damaged mucous membranes and central venous catheters through colonization (2). This case emphasizes how difficult it is to distinguish between invasive bacterial infections and fungal infections in patients with severe neutropenia, as well as that skin infections can be associated with *S. maltophilia*.

Case Report

An eight-year-old girl was admitted to the hospital because of fever, bone and joint pain for 3 months. Physical examination revealed paleness, painful movement in the right hip joint and lack of organomegaly. Laboratory studies showed leukocytosis of 93.000/mm^3, hemoglobin of 9.9 g/dL, and a platelet count of 117.000/mm^3. A bone marrow aspiration established a diagnosis of acute lymphoblastic leukaemia (ALL), and chemotherapy was started (ALL IC-BFM 2009). On the 15th day of induction therapy, a Hickman catheter was inserted to act as a venous catheter. On the 55th day of induction therapy, she developed severe neutropenia. On the 60th day of induction chemotherapy, her body temperature increased to 39 °C. A complete blood count showed a white blood cell count of 300/mm^3, an absolute neutrophil count of 0, and C-reactive protein

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(CRP) 0.31 mg/dL (normal range 0-0.8). Therefore, she was considered to have febrile neutropenia at that time. In accordance with the clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America guidelines, antibiotic therapy was initiated with carbapenem, aminoglycoside, and vancomycin. Her fever continued for 5 days CRP: (15.5 mg/dL), and so Liposomal Amphotericin B was added to the therapy. On day 7 of febrile neutropenia, physical examination revealed a hyperaemic, tender, irritable and non-fluctuating lesion in the perianal region, which was seen as cellulitis. Its size increased to 5x6 cm. The pelvic magnetic resonance imaging revealed a suprasphincteric and superficial perianal fistula in the right perianal region (Figure 1). The biopsy from her lesion couldn't be done because of bacteremia risk from the infected area due to severe neutropenia. Due to persistent fever, carbapenem was stopped and colistin initiated. Galactomannan antigen test result was positive with a level of 2.3 on the 9th day of febrile neutropenia. Since invasive aspergillosis could not be ruled out, voriconazole was added. Four days after the development of the lesion in the perianal region, pain started

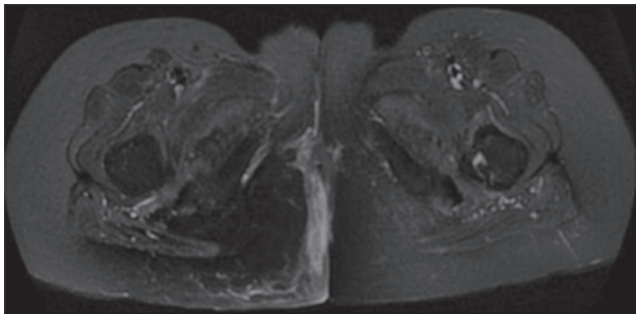

Figure 1. Pelvic magnetic resonance imaging showed a cellulitis in the right perianal region

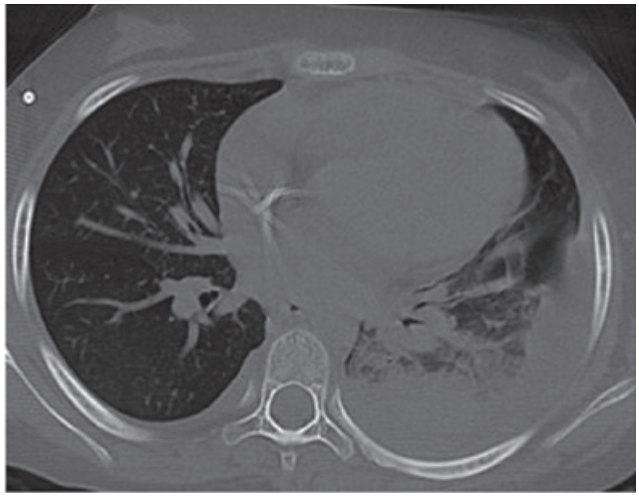

Figure 2. Thorax computed tomography showed a pneumonic consolidation and pleural effusion in the left lower pulmonary lobe

in the left side of the chest. Thorax computed tomography revealed pneumonic consolidation and pleural effusion in the lower left lobe (Figure 2). Her galactomannan antigen titre began to decrease 4 days later (0.9). Catheter cultures were negative. *S. maltophilia* was isolated in two blood cultures. Trimethoprim-sulfamethoxazole (15 mg/kg/day, parenterally) was initiated. According to culture antibiogram results, ciprofloxacin was also added. Consolidation developed in the upper right lobe of the lung, subsequently. Within a few days, the patient developed respiratory failure. Despite aggressive supportive therapy, the patient's condition deteriorated and she died 7 days later.

After receiving informed consent, a lung necropsy was performed, two from the left lung and one from the right lung. Pathological investigation revealed no fungal spores or hypha; massive intra-alveolar haemorrhage was also detected. Post-mortem catheter and blood cultures were negative. Written informed consent was obtained from the patient's parents.

Discussion

Patients with haematological disorders, particularly leukemic patients, are in a high-risk group for *S. maltophilia* infections, due to chemotherapy-associated neutropenia and immunodeficiency (2). Use of wide-spectrum antibiotics and long-term catheterization increases this risk (3). Our patient had an underlying disease of ALL as a haematological malignancy, and was on immunosuppressive treatment. A history of hospitalization for 60 days, with wide-spectrum antibiotics for 10 days for neutropenic fever, must be noted. In addition, the patient had a central venous catheter and multiple risk factors for *S. maltophilia*.

S. maltophilia is associated with an increasing number of infections at various sites, particularly pneumonias, bacteremias and cellulitis (4) In patients with severe immunodeficiency, it is described as a haemorrhagic pneumonia pathogen, and does not have characteristic radiographic features that can be differentiated from other bacterial pneumonia. Its radiologic appearance may exhibit a unilateral or bilateral pattern, but it is rarely accompanied by pleural effusion (4). The clinical findings resemble those of pulmonary aspergillosis (5). Generally, cough and dyspnea frequently accompany it, which may manifest with pleuritic chest pain and haemoptysis (6). Our patient had chest pain symptoms, although radiological investigation revealed no specific finding as the causative agent.

Galactomannan is the polysaccharide, which is the building block of the cell wall of aspergillosis and other types of fungus. In some patients, clinical signs and symptoms of invasive aspergillosis can be demonstrated before appearing. False positive results can also occur due to the colonization of the airways by the aspergillosis species (7). In our patient,

we did not see a test result to support fungal infection, other than galactomannan positivity. A low galactomannan titre reduced the possibility of a fungal infection diagnosis, while the positive galactomannan antigen test was thought to be aspergillosis colonization of the respiratory tract.

The most remarkable type of soft tissue infection due to *S. maltophilia* is the metastatic cellulitis, primary cellulitis, infected mucocutaneous ulcers and ecthyma gangrenosum (1,8-10). A study of 114 patients with malignancies and *S. maltophilia* infection reported metastatic cellulitis in 6 patients, primary cellulitis in 5 patients and infected mucocutaneous ulcers in six patients (1). Moser et al. (8) reported skin infections in three of 13 neutropenic patients with *S. maltophilia* bacteremia. They reported tender, erythematous, warm subcutaneous nodules, suggesting cellulitis in one patient, tender, red, warm, poorly-demarcated subcutaneous lesions resembling cellulitis in another, and well-demarcated skin lesions resembling cellulitis in a third patient. Mucocutaneous infection by *S. maltophilia* consisted of infected ulcers of the gingiva, lips and buccal mucosa. So far, 10 cases were reported, including 4 cases which were associated with metastatic lesions (1,8,10).

In conclusion, *S. maltophilia* is an opportunistic pathogen with a high mortality rate in immunocompromised patients. Rarely, it may cause skin infections, such as subcutaneous nodules and metastatic cellulitis. In our patient, colonization of bacteria through the fistula area led to a breach of the mucosal barrier in the anal region, and may therefore have caused bacteremia and pneumonia. A long-term history of hospitalization, persistent fever (despite broad-spectrum antibiotics), pneumonia and skin infections associated with haematological malignancy in patients with *S. maltophilia* infection must be considered.

Ethics

Informed Consent: Consent form was obtained from the patient's parents.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: Z.C.Ö., A.B.T., Design: Z.C.Ö., Ö.B., Data Collection or Processing: Z.C.Ö., Analysis or Interpretation: Z.C.Ö., Ö.B., A.B.T., Literature Search: Z.C.Ö., A.B.T., Writing: Z.C.Ö.

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

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

References

1. Vartivarian SE. Papadakis KA, Palacios JA, Manning JT Jr, Anaissie EJ. Mucocutaneous and soft tissue infections caused by Xanthomonas maltophilia. A new spectrum. Ann Intern Med 1994;121:969-73.
2. Abbott IJ, Slavin MA, Turnidge JD, Thursky KA, Worth LJ. Stenotrophomonas Maltophilia: emerging disease patterns and challenges for treatment. Expert Rev Anti Infect Ther 2011;9:471-88.
3. Apisarnthanarak A, Mayfield JL, Garison T, et al. Risk factors for Stenotrophomonas Maltophilia bacteremia in oncology patients: a case–control study. Infect Control Hosp Epidemiol 2003;24:269-74.
4. Dignani MC, Grazziutti M, Anaissie E. Stenotrophomonas Maltophilia infections. Semin Respir Crit Care Med 2003;24:89-98
5. Maschmeyer G, Haas A and Cornely OA. Invasive aspergillosis: epidemiology, diagnosis and management in immunocompromised patients. Drugs 2007;67:1567-71.
6. Mori M, Tsunemine H, Imada K, Ito K, Kodaka T, Takahashi T. Life-threatening hemorrhagic pneumonia caused by Stenotrophomonas Maltophilia in the treatment of hematologic diseases. Ann Hematol 2014;93:901-11.
7. Maertens J, Maertens V, Theunissen K, et al. Bronchoalveolar lavage fluid galactomannan for the diagnosis of invasive pulmonary aspergillosis in patients with hematologic diseases. Clin Infect Dis 2009;49:1688-93.
8. Moser C, Jonsson V. Thomsen K, Albrectsen J, Hansen MM, Prag J. Subcutaneous lesions and bacteremia due to Stenotrophomonas Maltophilia in three leukemic patients with neutropenia. Br J Dermatol 1997;136:949-52.
9. Teo WY, Chan MY, Lam CM, Chong CY. Skin manifestation of Stenotrophomonas Maltophilia-A case report and review article. Ann Acad Med Singapore 2006;35:897-900.
10. Son YM, Na SY, Lee HY, Baek JO, Lee JR, Roh JY. Ecthyma Gangrenosum: A rare cutaneous manifestation caused by of Stenotrophomonas Maltophilia in a leukemic patient. Ann Dermatol 2009;21:389-92.

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Case Report

A Rare Cause of Gross Hematuria in Childhood: Renal Lymphangiectasia

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ABSTRACT

Renal lymphangiectasia is a rare disorder characterized by cystic malformation of the lymphatic ducts surrounding the kidney. In this article, an adolescent who presented with painless gross hematuria, hypertension, polycythemia and who was determined to have left perirenal lymphangiectasia and ipsilateral decreased renal function on imaging studies is reported.
Keywords: Renal lymphangiectasia, child, hematuria

Introduction

Renal lymphangiectasia (RL) is a rare benign malformation of the lymphatic system surrounding the kidney. It is characterized by a cystic dilatation of the peripelvic (intrarenal) and/or perirenal lymphatic ducts due to a miscommunication between the renal - perirenal lymphatic ducts and the retroperitoneal lymphatic trunks. It is bilateral in more than 90% of cases. The etiology of this disorder remains unknown, nevertheless, familial, developmental and acquired causes have been presumed (1,2).

RL is incidentally detected in most cases, however, it may have non-specific presentation such as abdominal pain, flank pain, hematuria and, rarely lymphedema, ascites or pleural effusion. Although benign, it may be complicated by hypertension, polycythemia, chronic renal failure or renal vein thrombosis (3-6).

Herein, we report a pediatric case who presented with gross hematuria, hypertension, polycythemia and ipsilateral decreased renal function probably linked to local compression of unilateral perirenal lymphangiectasia.

Case Report

A 13 year-old boy was referred to our clinic with painless gross hematuria which had been present for the previous 2 days without any other symptoms. He had no remarkable medical or family history. There was no history of trauma. Physical examination was normal except for mild hypertension. His blood pressure was 130/90 mmHg and was above the 95th percentile value for age, sex and height. Twenty-four-hour ambulatory blood pressure (ABP) monitoring was also performed and mean systolic and diastolic BP values were found >95th percentile of the ABP norm (stage 1 hypertension). A complete blood count showed polycythemia, with red blood cell (RBC): 5.7x10^{6}/mm^{3} (4.1-5.2 x10^{6}/mm^{3}), hemoglobin: 17.2g/dL (12.8-15.0 g/dL), hematocrit: 51% (37.3-47.3%), mean corpuscular volume: 90 fL (81.4-91.9

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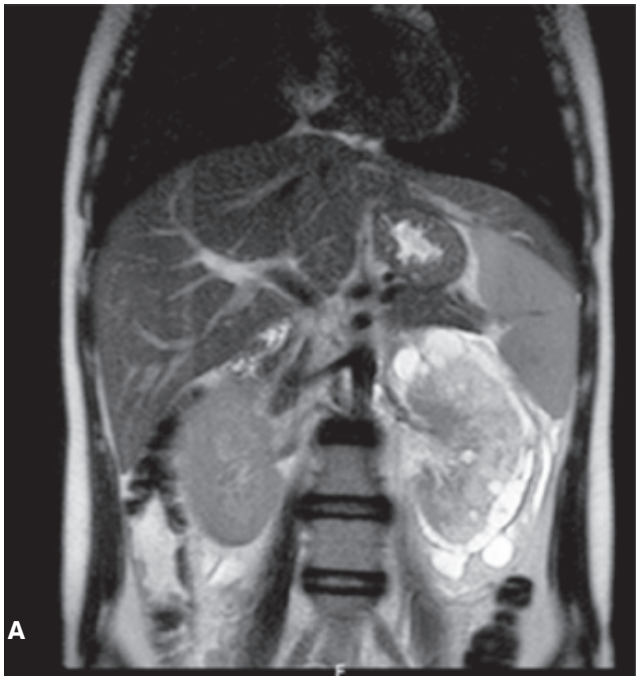
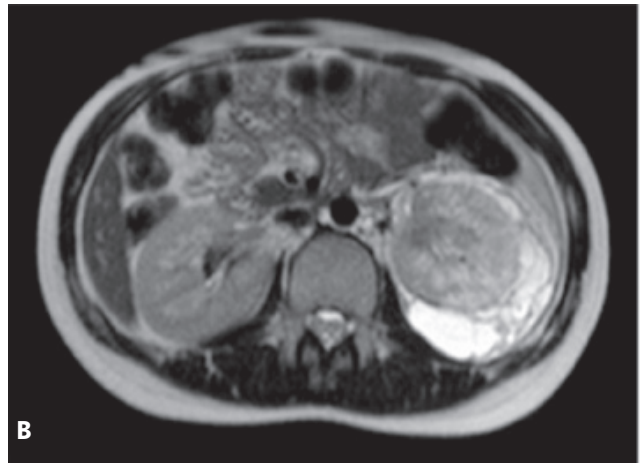
fL). Routine biochemical analysis, including renal function parameters and serum renin level were within normal ranges. His urine was reddish and urinalysis revealed proteinuria 1+, RBC 3+.

Ultrasonography (US) revealed the left kidney with increased parenchymal echogenicity and multi septated perinephric collection. Abdominal magnetic resonance imaging on T2A weighted images revealed a multilocular hyperintense cystic lesion infiltrating renal parenchyma and surrounding the left renal cortex. The perirenal cysts were hypointense and non-contrast enhancing on T1 weighted images (Figure 1 A,B,C). The right kidney was normal in all imaging studies. These characteristic radiological imaging findings were consistent with the appearance of left perirenal lymphangiectasia. In addition, left kidney differential function was found to be 27% by dimercaptosuccinic acid renal scintigraphy. No pathological finding was detected in renal doppler US, including left renal vein dilatation. Thus, the diagnosis of nut-cracker phenomenon was also ruled out.

The diagnosis of left perirenal lymphangiectasia was made on the basis of clinical, imaging and laboratory findings that were summarized above. The patient was managed conservatively. Angiotensin-converting enzyme (ACE) inhibitor (enalapril maleate, 0.3 mg/kg/day in 2 divided doses) was started for hypertension. On follow-up, gross hematuria was improved spontaneously and urinalysis returned to normal. After one month of enalapril therapy, his blood pressure lowered to the normal range. His hematocrit values were stable and phlebotomy was not required. The left hypo-functioning kidney did not affect global renal function. Controlled ultrasounds did not show an increase in perirenal collection on the left kidney. Written informed consent was obtained from patient's parents for publication.





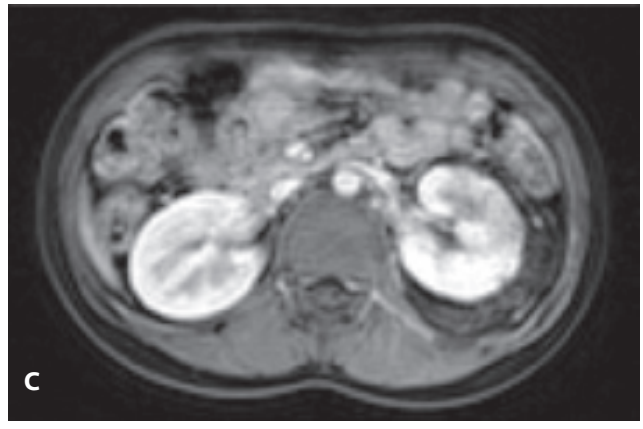


Figure 1. A) Hyperintense left perirenal cystic lesion infiltrating renal parenchyma on coronal T2 weighted magnetic resonance image, B) Hyperintense left perirenal multiple cysts on axial T2 weighted image, C) Axial post-contrast T1 fat-suppressed image showing hypointense and non-contrast enhancing left perirenal cysts

Discussion

In the literature, cystic RL has been more rarely described in childhood than in adulthood and it may be symptomatic in any pediatric age group including the neonatal period (7).

To our knowledge, gross hematuria as the initial manifestation of RL in childhood has been first described in our case. Similarly, although hypertension and polycythemia associated with RL are seen in adults, this association has been first reported in a pediatric case (8). The cause of both conditions is suggested to be the compression of the renal parenchyma by subcapsular collection, which results in increased erythropoietin and renin secretion due to ischaemic kidney (page kidney).

In our case, the serum renin level was normal, however, since needle aspiration of the left perirenal collection was not

performed, we do not know the renin level in the perinephric fluid. We were also unable to detect the serum erythropoietin concentration in our center. Nevertheless, the left perinephric collection was compressing the kidney on imaging studies. Also, his high blood pressure was under control by an ACE inhibitor. Therefore, we attributed both the hypertension and polycythemia to ischaemic kidney due to compression of the left perirenal collection.

In most patients, symptoms associated with RL improve following conservative treatment as in our case. ACE inhibitors are proposed for the treatment of renin-dependent hypertension. Marsupialization or needle aspiration of the perinephric fluid can be performed for large perinephric collections. Asymptomatic patients do not require treatment.

In conclusion, RL is a rare cause of cystic renal diseases in the pediatric age group and its diagnosis is based primarily on pathognomonic imaging findings. Treatment of complications and long-term follow-up are required to reduce renal morbidity in symptomatic patients.

Ethics

Informed Consent: Written informed consent was obtained from the patient's parents.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: Ç.S.D., Design: Ç.S.D., G.K.A., Data Collection and/or Processing: Ç.S.D., G.K.A., Literature Search: Ç.S.D., G.K.A., Writing: Ç.S.D.

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

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

References

1. Pandya VK, Sutariya HC, Gandhi SP, Khemchandani SI, Patel HV, Shah MK. Role of CT scan in diagnosis of renal lymphangiectasia: our single-center experience. Ren Fail 2017;39:533-9.
2. Nassiri AA, Lotfollahi L, Bakhshayeshkaram M, et al. Renal Lymphangiectasia: A Curious Cause of Pleural Effusion. Tanaffos 2015;14:213-6.
3. Arora R. Bilateral renal lymphangiectasia-an unusual cause of abdominal distension and flank pain in a child. Quant Imaging Med Surg 2016;6:466-9.
4. Cadnapaphornchai MA, Ford DM, Tyson RW, Lum GM. Cystic renal lymphangiectasia presenting as renal insufficiency in childhood. Pediatr Nephrol 2000;15:129-31.
5. Simonton SC, Saltzman DA, Brennom W, et al. Cystic renal lymphangiectasia: a distinctive clinicopathologic entity in the pediatric age group. Pediatr Pathol Lab Med 1997;17:293-301.
6. Ueda S, Yanagida H, Sugimoto K, et al. Chronic renal insufficiency in a boy with cystic renal lymphangiectasia: morphological findings and long-term follow-up. Clin Nephrol 2007;68:416-21.
7. Pickering SP, Fletcher BD, Bryan PJ, Abramowsky CR. Renal lymphangioma: a cause of neonatal nephromegaly. Pediatr Radiol 1984;14:445-8.
8. Blanc M, Schmutz G, Belzile F, Sabbagh R. Renal lymphangiectasia presenting with hypertension and polycythemia. Can Urol Assoc J 2014;8:163-6.

2018 Referee Index

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Oytun Hastürk
Özge Altun Köroğlu
Özgür Pirgon
Özlem Bağ
Özlem Tüfekçi
Özlem Ünal
Pelin Özlem Şimşek Kiper
Petek Bayındır
Pınar Gençpınar
Salih Çetinkurşun
Salih Kavukçu
Samim Özen
Sanem Yılmaz
Saygın Abalı
Selçuk Yüksel
Sema Kalkan Uçar
Semra Çetinkaya
Semra Gürsoy
Serap Akyüz
Serpil Erermiş
Sezen Köse
Süleyman Kalaycı
Şebnem Çalkavur
Şenay Savaş
Şule Gökçe
Tahir Atik
Tamer Tüzüner
Tolga İnce
Türkan Turan
Ünsal Yılmaz
Volkan Hazar
Yeşim Aydınok
Yeşim Öztürk
Zafer Dökümcü
Zeki Yüncü
Zeynep Ökte
Zülal Ülger
Zümrüt Başbakkal
Zümrüt Şahbudak Bal

2018 Author Index

2018 Author Index

2018 Subject Index

2018 Subject Index