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RESEARCH ARTICLE

# Insights into Childhood Obesity: Sleep Patterns, Vitamin D, and Metabolic Dynamics

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## ABSTRACT

**Objective:** The high prevalence of childhood obesity necessitates a deeper understanding of its underlying pathophysiological mechanisms and associated conditions to effectively address this public health concern. This study investigated the association between vitamin D levels, insulin resistance, dyslipidemia, and sleep patterns in the context of childhood obesity.

**Methods:** This study used data from 115 obese children and adolescents aged 9.9–18 years, identified by body mass index (BMI, kg/m$^2$) >95$^{th}$ percentile for the children receiving care at a Pediatric Endocrinology Outpatient Clinic. We collected sleep-related information, including onset time and duration, through direct parental questioning and compared these sleep patterns with key health indicators, such as vitamin D levels, insulin resistance, and dyslipidemia.

**Results:** Children who went to bed before 21:30 had the lowest mean HOMA-IR value (4.8±2.6), whereas children who slept between 21:30 and 23:00 (5.4±2.5) and after 23:00 (5.0±2.5) exhibited slightly higher values (p=0.374 and p=0.789, respectively). Similarly, children who went to bed earlier had lower mean levels of TC (158.7 mg/dl vs. 161.2 mg/dl), LDL (92.3 mg/dl vs. 95.6 mg/dl), and TG (84.1 mg/dl vs. 106.3 mg/dl) than those who slept later (p=0.743, p=0.619 and p=0.067, respectively). However, children who went to bed before 21:30 had significantly higher HDL levels (49.7 mg/dl vs. 44.3 mg/dl, p=0.019). Regarding sleep duration and 25(OH)D levels, 58.0 % of children with 25(OH)D levels <20 µg/L slept ≤7 hours, whereas 42.0 % slept ≥8 hours. In contrast, 73.5 % of children with 25(OH)D levels ≥20 µg/L slept ≥8 hours, whereas only 26.5 % slept ≤7 hours (p=0.003).

**Conclusions:** Earlier bedtimes and sufficient sleep duration are associated with reduced insulin resistance, more favorable lipid profiles, and higher vitamin D levels in obese children.

**Keywords:** Obese children, sleep time, sleep duration, vitamin D, insulin resistance

## INTRODUCTION

Childhood obesity is a global health concern with lasting implications because it increases the risk of obesity-related complications in adulthood. (1–3). Addressing the roots of childhood obesity is crucial in combating this health challenge (4). Beyond factors like poor dietary habits and reduced physical activity, attention is turning towards the influence of sleep disorders and vitamin D on metabolic imbalances (5). Investigating the complex interplay of these elements holds promise for comprehending the triggers of childhood obesity and advancing effective interventions.

Vitamin D [25(OH)D], known for its effects on calcium, phosphorus, and bone health, is closely linked to obesity and body mass index (BMI) (6). Studies have shown that adolescents with higher BMIs tend to have lower 25(OH)D levels (7,8). Moreover, vitamin D deficiency (<12 µg/L) is prevalent among obese individuals (9). Low levels of 25(OH)D may trigger hormonal responses that promote lipogenesis and obesity (10).

Vitamin D deficiency is also associated with sleep disorders because brain regions containing 25(OH)D receptors are involved in sleep regulation. (11). Low 25(OH)D levels have been linked to poor sleep quality and duration (12). Shortened sleep duration during childhood has been associated with higher rates of childhood obesity (13,14). These findings indicate a strong relationship between vitamin D insufficiency or deficiency, obesity, and sleep disorders.

Consistent with this view, recent studies have emphasized the potential influence of sleep and 25(OH)D on metabolic

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health. (15). Evidence suggests that inadequate sleep and 25(OH)D levels may negatively impact metabolism and insulin sensitivity. However, existing literature has mainly focused on adults, highlighting the need for more research to understand the interplay between sleep duration, timing, and obesity, especially in childhood obesity.

The present study investigated the potential associations between sleep patterns (i.e., sleep timing and duration), insulin resistance, dyslipidemia, and 25(OH)D levels in obese children. The findings of this study may contribute to the development of preventive strategies against obesity within the field of preventive medicine.

## MATERIAL AND METHODS

### Study population

This study included 115 obese children and adolescents aged 9.9–18 years who were under the care of the Pediatric Endocrinology Outpatient Clinic. To identify children with obesity, we relied on the body mass index (BMI). BMI was calculated using the formula body weight (kg) / (height)(m))$^2$, and patients with a BMI percentile above the 95th percentile for age and sex were included in the study. Moreover, patients with chronic systemic diseases, ongoing medication use, endocrinopathy, psychological disorders, or syndromic-monogenic obesity were excluded from the analysis.

The research was conducted during a specific period, from September 2018 to November 2018, which coincided with the autumn season in Turkey. During this period, data related to 25(OH)D levels were systematically collected. The collection procedures were carried out in the morning. Due to the patients' treatment schedules following sample collection, only a single sample per patient was obtained as part of the data collection process.

Subsequently, we assessed sleep-related data, including sleep onset time and sleep duration for the participants by direct questioning from their parents. The acquired data were meticulously documented on designated forms designed for this specific inquiry. All aspects of this study were executed in full compliance with ethical guidelines and regulations. Prior to the commencement of the study, an official endorsement was obtained from the ethics committee, which was in line with the principles outlined in the Declaration of Helsinki. Active efforts were made to inform the families of the participants about the study purposes and methods. Subsequently, formal informed consent was obtained from the families, thereby reinforcing ethical considerations in research practices.

### Measures

Anthropometric measurements including weight, weight z-score, height, height z-score, BMI, BMI percentile (BMI %), and BMI z-score were calculated and recorded during physical examinations, along with a comprehensive medical history. The patients' puberty status was determined according to the Tanner-Marshall scoring system, categorizing patients as P1 (prepubertal), P2-P4 (peripubertal), or P5 (postpubertal).

Various biochemical parameters were assessed in the study. Fasting blood glucose (FBG), fasting insulin, lipid profile [serum total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TG)], alanine aminotransferase (ALT), aspartate aminotransferase (AST), and 25(OH)D (ng/ml) levels] were analyzed. Vitamin D deficiency was defined as <12 µg/L, insufficiency as <20 µg/L, and sufficiency as ≥20 µg/L, according to established criteria. (16).

FBG levels were measured using the glucose hexokinase method. Serum TC was quantified enzymatically using the oxidase method, whereas HDL and TG levels were measured using a homogenic enzymatic method on Roche Modular (Germany) automatic biochemistry analyzers. LDL-C was calculated using the Friedewald formula [LDL-C = (TC – HDL-C) - TG/5] for triglyceride levels ≤400 mg/dl. For samples with TG levels >400 mg/dl, LDL-C was measured using a specific colorimetric enzymatic assay kit. Fasting insulin levels were assessed using the radioimmunoassay (RIA) method. ALT and AST were measured using the enzymatic UV colorimetric method on serum samples from blood specimens using Roche Cobas c 503 and Roche Cobas c 702 automated analyzers. Plasma samples collected in purple-top EDTA tubes were used to measure 25(OH)D using high-performance liquid chromatography (HPLC) method (Thermo Fisher Scientific, USA).

To evaluate insulin resistance, serum fasting insulin levels and the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) index were assessed. The HOMA-IR index was calculated using the formula [Fasting blood glucose (mmol/L) x Fasting Insulin (mIU/L)] / 22.5 (17). Given that HOMA-IR values can be influenced by factors such as ethnicity, age, and pubertal status, the study utilized established thresholds to determine insulin resistance: HOMA-IR values >2.22 for prepubertal girls, >2.67 for prepubertal boys, >3.82 for pubertal girls, and >5.22 for pubertal boys, as determined by Kurtoğlu et al. in the context of Turkish children (18). ALT and AST levels were measured in patients to assess the absence of liver enzyme dysfunction.

To assess the participants' sleeping habits in terms of both sleeping time and duration, we employed two distinct items. In our study cohort, three distinct peaks in sleep timing were observed. Accordingly, to measure sleep onset time, we used a 3-category variable that included the following periods: (i) before 21:30, (ii) between 21:30 and 23:00, and (iii) after 23:00. Based on the National Sleep Foundation's recommendations, which advise against less than 7 hours of sleep for school-aged children and teenagers, we divided sleep duration into two groups: (i) 4-7 hours and (ii) 8 hours or more. (19).

### Statistics

All data were analyzed using the STATA V.16 program. Descriptive statistics were expressed as mean ± standard deviation for normally distributed variables, median (min-max) for non-normally distributed variables, and number of cases and (%) for nominal variables. The significance of the difference between the groups was evaluated using Mann–Whitney U

test, Pearson's chi-square and Kruskal-Wallis test. A p value of less than 0.05 was considered statistically significant.

**RESULTS**

The descriptive statistics are summarized in Table 1 (Panels A and B), and the comparative statistics are presented in Table 2 (Panels C, D, E, F). Panel A of Table 1 provides a comprehensive overview of the demographic, anthropometric, and biochemical parameters under examination. A total of 115 obese children were included in the study. The mean values of parameters including age, weight (kg), weight z-score, height (cm), height z-score, BMI (kg/m$^2$), BMI%, and BMI z-score for the study cohort are provided in Panel A of Table 1.

Additionally, Table 1 Panel A presents the biochemical parameters of the 115 obese children who participated in the study. In the study group, 7.8% of the participants were classified as prepubertal, 39.1% as peripubertal (P2-P4), and 53.0% as postpubertal. These parameters include FBG, fasting insulin, ALT, AST, TC, LDL, HDL, TG, and 25(OH)D levels, along with the means and standard deviations of HOMA-IR values calculated according to pubertal status.

Furthermore, Panel B of Table 1 presents the percentage distribution of patients according to sleep timing and sleep duration.

The mean HOMA-IR values within distinct sleep timing categories are shown in the three groups in Panel C of Table 2. The group that slept before 21:30 (the reference group) exhibited the lowest mean HOMA-IR value at 4.8 ± 2.6. Comparatively, those who slept between 21:30 and 23:00 h demonstrated a slightly higher mean HOMA-IR value of 5.4 ± 2.5 (p=0.374), whereas those who slept after 23:00 h displayed a mean HOMA-IR value of 5.0 ±2.5 (p=0.789).

In order to investigate the relationship between sleep timing and dyslipidemia parameters, a two-group analysis was undertaken for enhanced comparability, as shown in Panel D

**Table 1. Descriptive Statistics of Demographic, Anthropometric, Biochemical Parameters, and Sleep Patterns**

| **Panel A: Demographic, Anthropometric, and Biochemical Parameters** | | |
|---|---|---|
| **Parameter** | **Mean (± Standard deviation in parentheses)** | |
| **Age (decimal year)** | 13.2 (±2.2) | |
| **Weight (kg)** | 72.3 (±16.6) | |
| **Weight z score** | 2.2 (±1.05) | |
| **Height (cm)** | 158.4 (±9.3) | |
| **Height z score** | 0.5 (±1.0) | |
| **Body mass index (BMI, kg/m$^2$)** | 28.5 (±4.3) | |
| **Body mass index % (BMI %)** | 97.1 (±3.0) | |
| **Body mass index z score (BMI z score)** | 3.0 (±1.0) | |
| **Fasting blood glucose (FBG, mg/dl)** | 86.4 (±7.1) | |
| **Fasting insulin (mIU/ml)** | 23.6 (±10.7) | |
| **Alanine aminotransferase (ALT, U/L)** | 18.2 (±9.3) | |
| **Aspartate aminotransferase (AST, U/L)** | 20.5 (±5.0) | |
| **Total cholesterol (TC, mg/dl)** | 160.8 (±27.4) | |
| **Low-density lipoprotein (LDL, mg/dl)** | 95.1 (±23.2) | |
| **High-density lipoprotein (HDL, mg/dl)** | 45.0 (±8.2) | |
| **Triglycerides (TG, mg/dl)** | 103.4 (±43.8) | |
| **HOMA-IR** | 5.2 (±2.5) | |
| **Vitamin D (25(OH)D) (µg/L)** | 16.6 (±8.5) | |
| **Panel B: Descriptive statistics of sleeping patterns (timing and duration)** | | |
| **Sleep timing** | **N** | **Percentage (%)** |
| **Before 21:30** | 15 | 13.0 |
| **21:30-23:00** | 53 | 46.1 |
| **After 23:00** | 47 | 40.9 |
| **Sleep duration** | **N** | **Percentage (%)** |
| **4-7 hours** | 56 | 48.7 |
| **7 hours or more** | 59 | 51.3 |

**Table 2. Comparative Analysis of Sleep Patterns and Metabolic Parameters (Mean ± Standard Deviation in parentheses)**

| **Panel C: HOMA-IR Levels according to Sleep Timing (Three Groups)** | | | |
|---|---|---|---|
| **Group** | **HOMA-IR* (Mean ±SD)** | **P-value** | |
| **Before 21:30** | 4.8 (± 2.6) | Reference | |
| **21:30–23:00** | 5.4 (± 2.5) | 0.374 | |
| **After 23:00** | 5.0 (± 2.5) | 0.789 | |
| **Panel D: Lipid Profile Parameters according to Sleep Timing (Two Groups)** | | | |
| **Parameter** | **Before 21:30 (Mean ± SD)** | **After 21:30 (Mean ± SD)** | **P-value** |
| **Total cholesterol level (mg/dL)** | 158.7 (± 23.8) | 161.2 (± 28.1) | 0.743 |
| **LDL* (mg/dL)** | 92.3 (± 22.2) | 95.6 (± 23.5) | 0.619 |
| **TG* (mg/dL)** | 84.1 (± 39.4) | 106.3 (± 43.8) | 0.067 |
| **HDL* (mg/dL)** | 49.7 (± 10.4) | 44.3 (± 7.7) | 0.019 |
| **Panel E: 25(OH)D* Levels according to Sleep Timing (Three Groups)** | | | |
| **Group** | **25(OH)D (µg/L) (Mean±SD)** | **P-value** | |
| **Before 21:30** | 20.3 (± 8.2) | Reference | |
| **21:30–23:00** | 15.7 (± 9.2) | 0.06 | |
| **After 23:00** | 16.5 (± 7.5) | 0.122 | |
| **Panel F: 25(OH)D Status according to Sleep Duration (Two Groups)** | | | |
| **Group** | **25(OH)D < 20 µg/L (%)** | **25(OH)D ≥ 20 µg/L (%)** | **P-value** |
| **4–7 hours** | 58 | 26.5 | Reference |
| **8 hours or more** | 42 | 73.5 | 0.003 |

*HOMA-IR: Homeostatic Model Assessment of Insulin Resistance, LDL: Low-density lipoprotein, TG: Triglycerides, HDL: High-density lipoprotein, 25(OH)D: Vitamin D

of Table 2 (findings based on three groups are also available upon request). We grouped the participants based on their sleep onset time: those who slept before 21:30 and those who slept after 21:30. Children who went to bed before 21:30 exhibited the following mean values for lipid profiles: TC 158.7± 23.8 mg/dl, LDL 92.3± 22.2 mg/dl, TG 84.1± 39.4 mg/dl; and HDL 49.7 ±10.4 mg/dl. In contrast, children who went to bed after 21:30 had higher mean values: TC 161.2 ±28.1 mg/dl, LDL 95.6 ±23.5 mg/dl, TG 106.3 ±43.8 mg/dl, and HDL 44.3± 7.7 mg/dl. Although the differences in TC, LDL, and TG levels were not statistically significant (p=0.743, p=0.619, p=0.067), the HDL levels were significantly higher in those who slept earlier (p=0.019).

Panel E of Table 2 examines the relationship between sleep timing and 25(OH)D levels. Participants who went to bed between before 21:30 had the highest mean 25(OH)D level at 20.3 µg/L, followed by those who went to bed after 23:00 at 16.5 µg/L and those who went to bed between 21:30 and 23:00 at 15.7 µg/L. These findings show that earlier bedtimes (before 21:30) are associated with higher 25(OH)D levels compared to later sleep timings. Although the mean 25(OH)D levels were higher in the earlier bedtime group, the differences did not reach statistical significance (p=0.06, p=0,122).

The analysis of the relationship between sleep duration and 25(OH)D levels (see Panel F of Table 2) revealed notable findings. Among individuals with 25(OH)D levels below 20 µg/L, 58.0% (n=47) reported a sleep duration of 7 hours or less, whereas 42.0 % (n=34) slept for 8 hours or more. In contrast, among individuals with 25(OH)D levels of 20 µg/L or higher, a lower proportion (26.5 % (n=9)) had a sleep duration of 7 hours or less, whereas the majority (73.5% (n=25)) slept for 8 hours or more. This difference was statistically significant (p=0.003).

## DISCUSSION

This study investigated the relationships between sleep timing, duration, and key metabolic markers, including insulin resistance (HOMA-IR), lipid profiles (TC, LDL, HDL, TG), and vitamin D levels [25(OH)D]. Given the growing evidence of sleep's role in regulating metabolic and endocrine functions, we hypothesized that sleep timing and duration may influence these markers.

Analyses of the relationship between sleeping time and HOMA-IR showed that going to bed earlier in childhood was associated with lower HOMA-IR levels. Although we did not find statistically significant differences, the trend of slightly lower insulin resistance values among those sleeping before 21:30 suggests that an earlier sleeping time has a potential positive impact on insulin resistance. This result is consistent with the findings of Reutrakul and Van Cauter. (20), who argued that the circadian system is linked to glucose metabolism. Although further research is required to fully elucidate the underlying mechanisms, given that many hormones exhibit circadian regulation, sleep disturbances can disrupt this rhythm. As a result, circadian rhythm misalignment is believed to contribute

to alterations in glucose metabolism, primarily through a reduction in insulin sensitivity (21,22). Likewise, individuals who go to bed earlier might have better alignment with their natural circadian rhythm, which could positively influence their metabolic processes (23,24).

The relationship between sleep timing and dyslipidemia parameters revealed significant trends. Specifically, individuals who retired to bed before 21:30 demonstrated lower mean levels of TC, LDL, and TG compared with those who slept later. However, the observed differences in TC, LDL, and TG did not reach statistical significance (p=0.743, p=0.619, p=0.067). Conversely, those who went to bed earlier exhibited significantly higher mean levels of HDL (p=0.019). These findings show that earlier sleep onset is associated with a more favorable lipid profile, which is characterized by reduced TC, LDL, and TG levels, alongside elevated HDL. Furthermore, these results agree with the existing literature highlighting the critical role of sleep timing, duration, and quality in modulating lipid metabolism. In a recent study, which examined the relationship between sleep timing, night sleep duration, and dyslipidemia, it was observed that individuals with later sleep timing had a higher risk of dyslipidemia. (25). A relevant study conducted by Smiley et al. (26) exemplified this connection, highlighting that prolonged sleep duration correlated with improved lipid profiles in adolescents.

The final phase of our analysis examined the relationship between sleep timing, sleep duration, and 25(OH)D levels. Although the differences between sleep timing groups were not statistically significant, our findings indicate a partial association, with earlier bedtimes higher 25(OH)D levels. Additionally, children who likely experienced insufficient sleep (i.e., 7 hours or less) tended to have lower 25(OH)D levels. These findings align with the existing literature examining the relationship between sleep duration and 25(OH)D levels, suggesting that increased sleep duration is associated with higher 25(OH)D concentrations (12,27,28). However, only few studies have investigated the relationship between sleep timing (bedtime) and 25(OH)D levels. For instance, a recent study by Al-Shawwa et al. (29) examined the relationship between 25(OH)D and sleep patterns in children. Their findings indicated that lower 25(OH)D levels were associated with adverse sleep outcomes, such as reduced sleep duration and delayed sleep onset. The observed relationship between sleep and 25(OH) D levels improves our understanding of how sleep habits influence broader health outcomes. Specifically, the findings suggest that sleep patterns may not only affect metabolic factors, such as insulin resistance, and have implications for other aspects of health.

**Limitations of the Study**

This study has several important potential limitations. First, sleep timing and duration were based on parental reports, which may have introduced bias. Parents may not know the exact bedtime. Second, the study did not collect information regarding the presence of sleep disorders, which could have influenced the results. In addition, some of our analyses' results were not statistically significant. We hypothesized that significant findings could be obtained using a larger sample size. Therefore, future research should involve a larger cohort to further explore these relationships. Furthermore, the observed relationships should be interpreted with caution because they are correlational rather than causal and may be influenced by confounding factors. For instance, sleep patterns may correlate with lifestyle factors such as diet and exercise, complicating efforts to isolate the direct effects.

## CONCLUSION

Our analysis, which included both statistically significant and non-significant findings, consistently supports the hypothesis that earlier sleep onset is associated with improved metabolic health. Specifically, earlier bedtimes were linked to reduced insulin resistance, more favorable lipid profiles, and potentially higher vitamin D levels. Additionally, children who experienced insufficient sleep (defined as ≤7 hours per night) tended to have lower vitamin D levels, emphasizing the broader implications of sleep duration on metabolic and endocrine health. These findings underscore the critical role of sleep in maintaining metabolic homeostasis.

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RESEARCH ARTICLE

# Psychometric Properties of the Turkish Oral Health Behavior Questionnaire for Adolescents Based on the Health Belief Model

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## ABSTRACT

**Objective:** To identify oral and dental health behaviors as critical life skills for adolescents. This study examined the Turkish psychometric properties of the "Health Belief Model-Based Oral Health Behavior Questionnaire for Adolescents" (OHBQAHBM).
**Methods:** This was a methodological study. The study sample consisted of 335 adolescents aged 13–18 years. The Sociodemographic Information Form and OHBQAHBM were used to gather data. The data analysis and evaluation were performed using factor analysis, Cronbach's alpha, and item-total score correlation.
**Results:** Thirty-five items were recorded on the main scale, and the other items were recorded on six subscales. The six subscales had a variance of 50.4%. The Turkish Cronbach's alpha coefficient was 0.880. Because of confirmatory factor analysis, the model fit index results were recorded as follows: 0.048 as the RMSEA, 0.861 as the goodness-of-fit index, and 0.924 as the comparative fit index.
**Conclusions:** The measurement tool was valid and reliable for evaluating adolescents' oral and dental health behaviors based on their health belief model.

**Keywords:** Health belief model, oral health behavior, adolescent health, scale validity, reliability

## INTRODUCTION

Adolescence, the pivotal stage from childhood to adulthood, is a crucial period for establishing health behaviors that often persist into adulthood. This transitional phase is particularly important for health protection and enhancement. The growing emphasis on social appearance during adolescence heightens interest in oral and dental health (ODH) among adolescents. However, they require support and guidance to sustain and enhance their health behaviors they acquire during this period (1-3).

The ODH is an essential indicator of overall health and quality of life (4,5). Poor oral hygiene and dental caries negatively affect physical, mental, and social well-being by causing eating, chewing, and speaking problems and pain (6). In addition, the long duration of dental treatments and high cost create a socioeconomic disadvantage that is challenging for adolescents and their families (7). Therefore, protective behaviors toward ODH reduce long-term health costs (8).

Adolescents believe brushing alone is sufficient to protect against ODH, and they delay regular dental checkups for various reasons(9). Due to dental anxiety and the high cost of dental treatment, adolescents are less likely to attend regular dental checkups (10-12). Therefore, toothbrushing alone is the most common behavior perceived as an individual responsibility for ODH. Regular toothbrushing is associated with the desire to retain white rather than healthy teeth (13). This indicates that adolescents' esthetic concerns outweigh their health. Adolescents should develop dental control behaviors in addition to regular toothbrushing to improve ODH. Many theories are mentioned in the literature as methods of gaining this behavior (14), and one of the most important of these theories is the health belief model (HBM) (15,16).

The HBM provides a holistic view of health behaviors. The framework comprises six main concepts: perceived susceptibility, perceived benefits, perceived severity, perceived barriers, cues to action, and self-efficacy. The model's concepts of the model guide the development of health behavior and the provision of its permanence. Therefore, the HBM is used in behavior development in many areas (17).

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Initiatives based on the HBM to change ODH behaviors have shown very successful results (18-20). Current measurement tools for assessing adolescents' ODH behavior are limited. For this reason, there is a need for measurement tools that can determine the factors that facilitate the emergence of adolescents' attitudes and behaviors toward ODH and identify barriers to maintaining these behaviors. The best way to demonstrate this is to develop a scale based on the six concepts of the HBM. The literature review did not identify a Turkish scale based on the HBM (18-20). The study aim was to investigate the Turkish psychometric properties of the "Oral Health Behavior Questionnaire for Adolescents Based on the Health Belief Model (OHBQAHBM)" (12).

## MATERIAL AND METHODS

### Study Design and Participant

A methodological, descriptive, and cross-sectional design was used. In methodological type studies, it is examined whether the scales developed in different cultures measure concepts in the same way in the culture to which they want to be adapted. The scale evaluates whether it is valid and reliable in the culture to which it is intended to be adapted. For this purpose, scale translation is performed, content validity is performed, pilot application is carried out, and construct validity is evaluated. All the steps were carried out in this study (21-26). The study sample consisted of healthy adolescents aged 13-18 years. Study data were collected using a "Sociodemographic Information Form" and the "Oral Health Behavior Questionnaire for Adolescents Based on the Health Belief Model" between April and June 2022. The data were collected face-to-face in the classroom environment from students in two public high schools in Izmir, western Turkey. The parents of the adolescents participating in the study were informed about the study, and written informed consent was obtained. In addition, the adolescents participating in the study were given detailed information about the research in the classroom, and their written informed consent was obtained. Validity and reliability analyses were conducted using the responses of students who agreed to participate in the study and completed the questionnaire.

The literature suggests that a sample of 5-10 times the number of items on the scale should be reached to test the validity and reliability of measurement tools. For this reason, it was necessary to include at least 175 adolescents, as there were 35 questions on the measurement tool of the study. In addition, since 27% upper/lower group analysis was used for discrimination analysis in this study, additional sample calculation was based on a t-test in independent groups in the GPOWER program, and the required sample size was determined as 320 adolescents at a significance level of 0.01% and 99% power. A total of 350 adolescents were planned to be included in the study sample to accurately demonstrate the validity and reliability of the scale. Within the scope of our research, 335 students who completed the data forms comprised the research sample (21-26).

### Instruments

***Adolescent Descriptive Information Form:*** This form consists of questions about sociodemographic characteristics (such as age, gender, class level, and economic level) and questions evaluating ODH behaviors. Questions about ODH behaviors include the frequency of daily toothbrushing, toothbrush change time, dental floss use, and frequency of dentist visits. The researchers prepared the questions.

***Oral Health Behavior Questionnaire for Adolescents Based on the Health Belief Model:*** This scale was developed by Xiang et al. (12), and its validity and reliability in adolescents were examined. This study consists of 35 items designed in 5-point Likert-type and six sub-dimensions. The total variance explained by the scale was 62.47%. The subdimensions explained variance rate varied between 3.98% and 24.79%. The factor loads ranged from 0.32 to 0.92. In the CFA, the fit indices were >0.90, and the RMSEA was <0.08. The item-total score correlation was 0.47–0.91. Cronbach's alpha coefficient for the six subdimensions of the scale ranged from 0.81 to 0.97. The sub-dimensions and the item distribution of the scale are as follows: "perceived susceptibility sub-dimension" (2 items); "perceived benefits sub-dimension" (7 items); "perceived barriers sub-dimension" (6 items); "cues to action sub-dimension" (3 items); "perceived severity sub-dimension" (7 items); "self-efficacy sub-dimension" (10 items). Scores on the scale ranged from 35 to 175. There are no reverse-scored items. A high score on the scale indicates a high level of health beliefs about ODH. The scale has no cut-off point (12).

### Translation of scale

The literature recommends that the most appropriate sentence structures and idioms be used in the target language and that sentences be adapted to the culture (21-24). For this purpose, the scale items in this study were translated into Turkish. The researchers translated the items into Turkish and created a Turkish version of the scale. Turkish was translated into English by a linguist fluent in both Turkish and English.

### Content validity of the scale

It is recommended that at least three experts be consulted to determine equivalence with the original scale in translated scales (22). Eight experts were consulted on the Turkish translation of the scale. Two of these experts were dentists, three were faculty members in pediatric nursing, and four were public health nursing faculty members. The original and translated scale forms were submitted to the experts together, and they were asked to score each item between 1 and 4 (1= needs a lot of change, 2= needs little change, 3= appropriate, and 4= very appropriate) to evaluate their suitability. The researchers revised the scale items in line with the experts' suggestions. The item-level content validity index (I-CVI) and the scale-level content validity index (S-CVI) were calculated for each item on the scale and the total scale. A rate of ≥0.80 in I-CVI and S-CVI indicates inter-rater agreement (25-27).

### Pilot application

It is recommended that the scale be applied to a group of 20-30 individuals with characteristics similar to those of study participants and who are not included in the sample to analyze the intelligibility of language and expressions (21,22). After the first translation phase, the scale was piloted to a sample of 20

people who were not included and had characteristics similar to those of individuals to whom the scale would be applied. The adolescents in the pilot application found the items intelligible and gave no negative feedback on the scale items. Therefore, the scale was applied to the main sample.

**Data analysis**

The data analysis used Cronbach's Alpha and McDonald's Omega to determine the scale's internal consistency and subdimensions. Pearson correlation analysis, inter-item correlation, and split-half analysis were used for the item total score analysis of the scale and subdimensions. Experts state that the minimum acceptable Cronbach's alpha value is 0.70 (21-24). The item-total score and item subscale total score correlation coefficients should be at least 0.20 (25-27). Response bias was evaluated using the Hotelling T-square test.

Explanatory and confirmatory factor analysis was used for construct validity. Explanatory factor analysis was performed to determine the item-factor relationship. The adequacy and suitability of data for factor analysis were examined using the Kaiser-Meyer-Olkin (KMO) coefficient and the Barlett Sphericity test. For factor analysis, the Barlett sphericity test value should be $p<0.05$ and that the KMO value should be >0.60. Principal axis factoring and Promax rotation were used to determine the scale's construct validity. Eigenvalues were accepted as ≥1 to choose the most appropriate structure and number of factors (25-27). Experts emphasize that the minimum factor value should be 0.32 (25,26). This study also accepted the minimum factor load of 0.32 to determine which items would be grouped under each factor (25-27).

Confirmatory factor analysis was used to determine whether the items and subdimensions explained the original scale structure. Multicollinearity analysis was performed before confirmatory factor analysis, and it was determined that there was no multicollinearity between items. The Pearson chi-square, degree of freedom, root-mean-square error of approximation (RMSEA), goodness of fit index (GFI), comparative fit index (CFI), and normal fit index (NFI) were examined. It is recommended that the chi-square value divided by the degree of freedom should be <5, RMSEA should be <0.080, and other fit indices should be >0.90 (25-26). The correlation matrix was used for explanatory factor analysis, and the covariance matrix was used for confirmatory factor analysis. The t-test was used for the upper-lower group comparison (27%. The error margin in the data evaluation was set at $p = 0.05$. The SPSS 24.0, AMOS 25.0, and JAMOVI 2.2 software packages were used for statistical analysis.

**Ethical consideration**

The approval of Dokuz Eylül University Non-Interventional Clinical Research Ethics Committee (IRB: 2022/17-03) and the permission of the Provincial Directorate of National Education in the province where the study was conducted were obtained. The parents of the adolescents participating in the study were informed about the study, and written informed consent was obtained. In addition, the adolescents participating in the study were given detailed information about the research in the classroom, and their written informed consent was obtained.

**RESULTS**

It was determined that 57.6% (n=193) of the students participating in the study were female, their mean age was 15.43+1,024 (min=13-max=18), 28.4% (n=95) were 9$^{th}$ graders, 36.4% (n=122) were 10$^{th}$ graders, and 10.4% (n=35) were 11$^{th}$ graders. In addition, 42.1% of mothers (n= 141) and 49.9% of fathers (n=167) had an undergraduate degree, 87.8% (n=294) of adolescents had a nuclear family, 79.4% (n=266) had equal income and expenses, 43.3% (n=145) brushed teeth at least twice a day, 20% (n=266) =70) changed their toothbrushes at least every three months, 60.9% (n=204) did not use dental floss, and 28.1% (n=94) went to the dentist regularly.

**Validity analyses**

Kaiser-Meyer Olkin's (KMO) coefficient was 0.859, and the $X^2$ value of the Bartlett test was 5743.381 ($p = 0.000$). Because of EFA, the scale consisted of six subdimensions. The first (self-efficacy) explained 20.993% of the total variance, the second (perceived benefits) subdimension 10.509%, the third (perceived severity) subdimension 7.479%, the fourth (perceived barriers) subdimension 4.703%, the fifth (cues to action) subdimension 4.406%, and the sixth (perceived susceptibility) subdimension 2.361%. The six subdimensions explained 50.451% of the total variance. The factor loads of the first sub-dimension varied between 0.692 and 0.826, the second sub-dimension between 0.686 and 0.835, the third sub-dimension between 0.439 and 0.774, the fourth sub-dimension between 0.462 and 0.691, the fifth sub-dimension between 0.459 and 0.826, and the sixth sub-dimension between 0.575 and 0.629 (Table 1).

**Table 1. The results of the explanatory factor analysis (n= 168)**

| Items | Faktor Loads | | | | | |
|---|---|---|---|---|---|---|
| | Self-efficacy | Perceived benefits | Perceived severity | Perceived barriers | Cues for action | Perceived susceptibility |
| I1 | | | | | | 0.575 |
| I2 | | | | | | 0.629 |
| I3 | | 0.686 | | | | |
| I4 | | 0.835 | | | | |
| I5 | | 0.815 | | | | |
| I6 | | 0.776 | | | | |
| I7 | | 0.700 | | | | |
| I8 | | 0.769 | | | | |
| I9 | | 0.686 | | | | |
| I10 | | | | 0.489 | | |
| I11 | | | | 0.462 | | |
| I12 | | | | 0.691 | | |
| I13 | | | | 0.483 | | |

The chi-square value of the six-factor model was 940.192, the degree of freedom was 535, and p = 0.000. The $X^2$/SD division was determined as 1.757. The following fit indices were obtained: RMSEA, 0.048; GFI, 0.861; CFI, 0.924; IFI, 0.925; TLI, 0.916; and NFI, 0.902. As CFA's result, first sub-dimension factor loads were found to vary between 0.70 and 0.80, second sub-dimension between 0.60 and 0.84, third sub-dimension between 0.39 and 0.80, fourth sub-dimension between 0.44 and 0.68, fifth sub-dimension between 0.51 and 0.81, and sixth sub-dimension between 0.62 and 0.64 (Table 2, Figure 1).

**Table 1. Continue**

| Items | Faktor Loads | | | | | |
|---|---|---|---|---|---|---|
| | Self-efficacy | Perceived benefits | Perceived severity | Perceived barriers | Cues for action | Perceived susceptibility |
| I14 | | | | 0.617 | | |
| I15 | | | | 0.647 | | |
| I16 | | | | | 0.459 | |
| I17 | | | | | 0.746 | |
| I18 | | | | | 0.826 | |
| I19 | | | 0.607 | | | |
| I20 | | | 0.631 | | | |
| I21 | | | 0.730 | | | |
| I22 | | | 0.774 | | | |
| I23 | | | 0.713 | | | |
| I24 | | | 0.558 | | | |
| I25 | | | 0.439 | | | |
| I26 | 0.752 | | | | | |
| I27 | 0.768 | | | | | |
| I28 | 0.736 | | | | | |
| I29 | 0.692 | | | | | |
| I30 | 0.826 | | | | | |
| I31 | 0.732 | | | | | |
| I32 | 0.785 | | | | | |
| I33 | 0.801 | | | | | |
| I34 | 0.735 | | | | | |
| I35 | 0.741 | | | | | |
| Variance explained (%) | 20.9 | 10.5 | 7.4 | 4.7 | 4.4 | 2.3 |
| Totoal Variance explained (%) | 50.4 | | | | | |
| KMO | 0.915 | | | | | |
| Bartlett $X^2$(p) | 1002.203 (p<0.001) | | | | | |

**Reliability analyses**

Cronbach's alpha coefficient of the total scale was determined as 0.880. The alpha value was determined as 0.930 for the first subdimension of the scale, 0.886 for the second subdimension, 0.795 for the third subdimension, 0.746 for the fourth subdimension, 0.694 for the fifth subdimension, and 0.605 for the sixth subdimension. The McDonald Omega coefficient of the total scale was 0.883, which was found as 0.930 for the first subdimension, 0.892 for the second subdimension, 0.824 for the third subdimension, 0.748 for the fourth subdimension, 0.737 for the fifth subdimension, and 0.615 for the sixth subdimension (Table 3).

Because of the split-half analysis, Cronbach's alpha values of the first and second halves were determined as 0.773 and 0.770, respectively. The correlation between the two halves was found to be 0.872. The Spearman-Brown coefficient was calculated as 0.932, and the Guttman split-half coefficients were 0.932 and 0.931, respectively. The inter-item correlation coefficients of the scale ranged from 0.161 to 0.735 (Table 3).

The Hotelling T-square test was employed to determine whether there was response bias in the scale, and the test

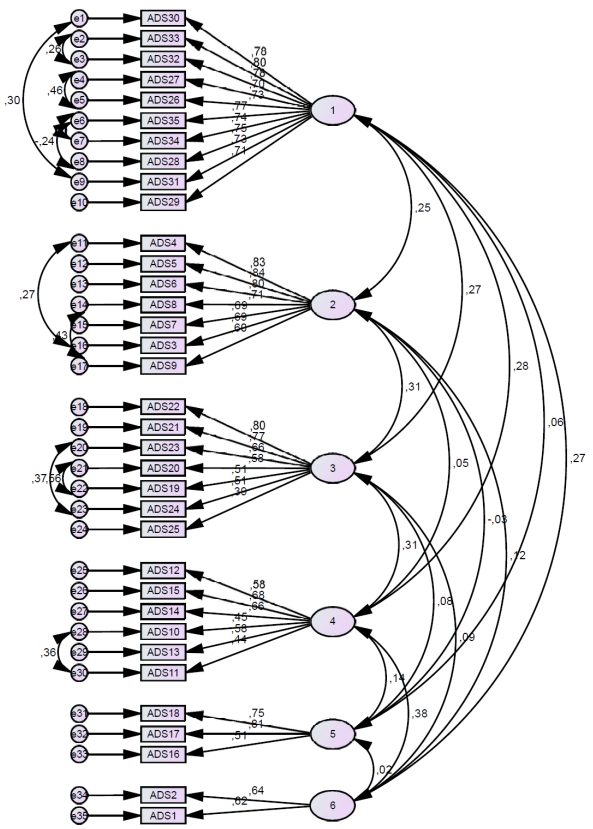


**Figure 1: Confirmatory factor analysis.**

**Table 2. Model fit indices of confirmatory factor analysis (n= 167)**

| | $X^2$ | DF | $X^2$/DF | RMSEA | GFI | CFI | IFI | TLI | NFI |
|---|---|---|---|---|---|---|---|---|---|
| Six-factor model | 940.192 | 535 | 1.757 | 0.048 | 0.861 | 0.924 | 0.925 | 0.916 | 0.902 |

DF: Degree of Freedom; RMSEA: Root Mean Square Error of Approximation; GFI: Goodness of Fit Index; CFI: Comparative Fit Index; IFI: Incremental Fit Index; NFI: Normed Fit Index; TLI (NNFI): Trucker-Lewis Index.

**Table 3. The results of the reliability analysis of the scale (n=335)**

| | | | Split-half analysis | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Cronbach Alpha | McDonald Omege | First Half Cronbach Alpha | Second Half Cronbach Alpha | Spearman Brown | Guttman's split half | Correlation Between the Two Halfs | M± SD (Min-Max) |
| Total Scale | 0.880 | 0.883 | 0.773 | 0.770 | 0.932 | 0.931 | 0.872 | 135.25+17.62 (79-175) |
| Self-efficacy | 0.930 | 0.930 | | | | | | 31.05+10.62 (10-50) |
| Perceived benefits | 0.886 | 0.892 | | | | | | 25.30+4.74 (6-30) |
| Perceived severity | 0.795 | 0.824 | | | | | | 30.19+4.37 (7-35) |
| Perceived barriers | 0.746 | 0.748 | | | | | | 23.75+4.56 (6-30) |
| Cues for action | 0.694 | 0.737 | | | | | | 12.68+2.69 (3-15) |
| Perceived susceptibility | 0.605 | 0.615 | | | | | | 7.97+1.74 (2-10) |

**Table 4. Corrected Cronbach's alpha, item-scale total score, and subdimension total score correlations when an item was deleted (n=335)**

| Items | Cronbach's alpha if item is deleted | Corrected Item-Total Score Correlation *(r)** | Corrected Item-Subscale Score Correlation *(r)** |
|---|---|---|---|
| I1 | 0.881 | 0.212 | 0.444 |
| I2 | 0.879 | 0.243 | 0.444 |
| I3 | 0.877 | 0.371 | 0.637 |
| I4 | 0.876 | 0.422 | 0.777 |
| I5 | 0.876 | 0.430 | 0.778 |
| I6 | 0.877 | 0.389 | 0.732 |
| I7 | 0.878 | 0.283 | 0.649 |
| I8 | 0.877 | 0.334 | 0.726 |
| I9 | 0.879 | 0.276 | 0.616 |
| I10 | 0.876 | 0.433 | 0.438 |
| I11 | 0.876 | 0.425 | 0.433 |
| I12 | 0.881 | 0.201 | 0.507 |
| I13 | 0.879 | 0.278 | 0.455 |
| I14 | 0.879 | 0.264 | 0.530 |
| I15 | 0.878 | 0.309 | 0.547 |
| I16 | 0.882 | 0.201 | 0.437 |
| I17 | 0.881 | 0.205 | 0.606 |
| I18 | 0.883 | 0.212 | 0.553 |
| I19 | 0.877 | 0.348 | 0.547 |
| I20 | 0.877 | 0.381 | 0.580 |
| I21 | 0.877 | 0.396 | 0.620 |
| I22 | 0.877 | 0.387 | 0.651 |
| I23 | 0.877 | 0.370 | 0.629 |

**Table 4. Continue**

| Items | Cronbach's alpha if item is deleted | Corrected Item-Total Score Correlation *(r)** | Corrected Item-Subscale Score Correlation *(r)** |
|---|---|---|---|
| I24 | 0.878 | 0.324 | 0.482 |
| I25 | 0.882 | 0.215 | 0.345 |
| I26 | 0.871 | 0.612 | 0.731 |
| I27 | 0.873 | 0.549 | 0.714 |
| I28 | 0.872 | 0.568 | 0.696 |
| I29 | 0.872 | 0.580 | 0.676 |
| I30 | 0.871 | 0.614 | 0.776 |
| I31 | 0.871 | 0.620 | 0.726 |
| I32 | 0.871 | 0.630 | 0.747 |
| I33 | 0.871 | 0.626 | 0.763 |
| I34 | 0.871 | 0.605 | 0.714 |
| I35 | 0.871 | 0.626 | 0.719 |

*** Significant at** p<.001, I =

**Table 5. Comparison of the total scale scores of the 27% lower and upper groups**

| Groups | M+SD | t | p |
|---|---|---|---|
| % 27 Lower Group (n=112) | 116.27+10.16 | 30.304 | <0.001 |
| % 27 Upper Group (n=112) | 154.61+8.720 | | |

values were found to be 1075.283, F = 28.501, and p = 0.000. The results of the analysis indicated that there was no response bias in the scale (Table 3).

The correlations of the scale items with the total scale score were 0.201–0.630. The correlations of the scale items with the

total subdimension score ranged from 0.345 to 0.766. None of the items significantly increased Cronbach's alpha values when deleted (Table 4).

The mean score of participants in the 27% lower group was 116.27 + 10.16, whereas the mean score of those in the 27% upper group was 154.61 + 8.72. The difference between the mean scores of the 27% upper and lower groups was statistically significant ($p<0.001$) (Table 5).

**DISCUSSION**

As a result of this study, it was determined that the adapted scale can be used to measure the oral-dental health behaviors of adolescents in Turkey in a valid and reliable manner. The study determined that the health belief model could be used effectively to measure the oral-dental health behaviors of adolescents.

In this study, whether the adapted scale can measure oral and dental health in a Turkish sample based on the health belief model and the similarity of the content of the original items with Turkish items were evaluated based on expert opinions. Experts stated that the scale preserved its original structure and could measure oral and dental health behaviors in Turkish adolescents based on the health belief model (26,27). The results of the analysis determined that the scale items were sufficient to measure adolescents' oral-dental health behaviors of adolescents.

In this study, EFA was used to evaluate whether the items formed subdimensions similar to those in the original scale. Because of EFA, it was determined that the scale had the same number of subdimensions as the original scale and that the items had the same subdimensions. It was determined that the factor loadings of the items in the scale were high and showed a high level of correlation with their subdimensions. These results demonstrated that the scale could measure the behaviors of adolescents toward oral and dental health accurately and sufficiently (12, 25, 26,28-31). The literature emphasizes that measurements were made using forms developed especially for evaluating oral and dental health. However, sufficient measurements could only be made if the models were based on them. In this study, the fact that the adapted scale was model-based and had a strong item-sub-dimension relationship proved that the scale could make adequate and accurate measurements (32-35). The EFA results revealed that the scale items were sufficient to measure the adolescents' oral and dental health and could be measured accurately without being confused with other concepts. The scale items were also related to oral and dental health.

Because of CFA in this study, it was determined that the structure determined by EFA and the dimensions under which the items were located were appropriate and compatible (26, 29,31). As a result of CFA, it was determined that the scale was sufficient in measuring the oral-dental health behaviors of adolescents in the Turkish sample, and the items adequately represented the subdimensions measuring oral-dental health. As a result of CFA, it was determined that the scale could adequately and accurately measure harmful behaviors toward oral-dental health, perceived wounds of behaviors, and self-efficacy levels, which are indicators for performing the behaviors. It is also suggested in the literature that scales prepared with the appropriate content can detect behaviors toward oral-dental health more accurately and adequately and that models should support these measurement tools. The results of this study provide suggestions for literature and support the literature (32-35).

Whether the scale makes similar measurements at different times and the relationship between the items are evaluated using internal consistency analyses. The most important of these is Cronbach's alpha. In the literature, alpha values are required to be 0.70 and above (28-31). In this study, alpha levels were >0.70 for the entire scale and subdimensions. The other analyses were the split-half and item-total score correlations. In all of these analyses, it was determined that the scale items were highly related to each other; the scale made similar measurements in different situations and had a strong conceptual structure. The literature emphasizes that it is essential for scales to have high internal consistency when measuring oral-dental health behaviors (28-35). It is emphasized that, especially in interventional studies, scales should be able to make accurate and sufficient measurements and should be consistent to define the change correctly (28-35). The reliability results in this study showed that the scale can provide high-level, consistent measurements and that its reliability is high. The high-reliability results in this study demonstrated that the scale could measure the oral-dental health behaviors of adolescents at different time points in a similar manner.

The results obtained in this study showed no response bias, and the measurement results were reliable. This result shows that people are not affected by external factors when answering the scale items and that they answer them according to their opinions. This result reveals that the validity and reliability of the scale are high (26-31).

Our study revealed a notable difference in the mean scores of adolescents between the upper and lower 27% groups.

These results showed that the scale had good discriminatory power and could adequately measure the area and distinguish between the 27% upper and lower groups. Scales with good validity and reliability should distinguish between individuals with positive and negative attitudes. For this purpose, a 27% lower-upper group analysis was performed. In this analysis, individuals with positive attitudes are expected to receive high scores, and individuals with negative attitudes are expected to receive low scores. The scales should be able to distinguish between these two groups and identify significant differences. The difference between the two groups in this study indicates that the scale is an accurate and reliable measurement.

There are a few limitations to this study. First, only adolescents who are voluntary to participate in the study. The second limitation is the use of convenience samples. However, keeping

the sample number high and collecting samples from different regions reduces the

## CONCLUSION

The results of the validity and reliability analyses conducted in this study indicate that the Oral Health Behavior Questionnaire for Adolescents Based on the Health Belief Model (OHBQAHBM) is an appropriate measurement tool for the Turkish sample. This scale can evaluate adolescents' attitudes toward ODH based on the HBM. Cross-cultural comparative studies can also be conducted using the scale. With this measurement tool, nurses can identify beliefs, attitudes, and behaviors that negatively affect adolescents' oral and dental health. This scale can be used to create intervention programs to achieve early acquisition of behaviors, such as regular toothbrushing, preventing uncontrolled sugary food consumption, and annual dental checkups. The results of this intervention can be monitored. ODH behaviors can be developed by identifying areas where adolescents are inadequate in terms of these behaviors and applying individual interventions. It was determined that this scale, whose validity and reliability was assessed, evaluated ODH multidimensionally and effectively. Therefore, the validity and reliability of the scale can be evaluated for the 6-12 age group.

**Ethics Committee Approval:** This study was approved by the ethics committee of Dokuz Eylül University Non-Interventional Clinical Research (IRB: 2022/17-03) and the permission of the Provincial Directorate of National Education.

**Informed Consent:** Written consent was obtained from the participants.

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RESEARCH ARTICLE

# The Effects of the COVID-19 Pandemic on Pubertal Development in Girls: A Retrospective Evaluation of Girls Presenting with Precocious Puberty Before and During the Pandemic

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## ABSTRACT

**Objective:** The timing of pubertal onset is a complex biological process influenced by various factors, many of which remain poorly understood. A notable increase in early puberty cases was observed during the COVID-19 pandemic. This study evaluated girls presenting with early or precocious puberty both during and in the five years before the pandemic.

**Methods:** Thirty-six girls (Group 1) with suspected early puberty during the COVID-19 pandemic (March 2020–July 2021) and forty girls (Group 2) diagnosed with central precocious puberty between 2015 and 2019 were included. Retrospective data on demographic, anthropometric, clinical, and laboratory findings were analyzed.

**Results:** The median (IQR) age at presentation was 8.07 (1.37) years in Group 1 and 7.89 (1.35) years in Group 2 (p=0.038). No significant differences were observed between the groups regarding height SDS, BMI-SDS, bone age, or Δ target height–predicted adult height SDS.

**Conclusions:** Despite a common association between obesity and early puberty, no differences in BMI were identified in this cohort. Environmental factors related to the pandemic conditions may have influenced the timing of puberty. Larger studies with broader populations are needed for definitive conclusions.

**Keywords:** COVID-19 pandemic, pubertal development, precocious puberty, girls

## INTRODUCTION

Central precocious puberty (CPP) is characterized by the early activation of the hypothalamic-pituitary-gonadal (HPG) axis, resulting in breast development in girls younger than 8 years and testicular enlargement in boys younger than 9 years (1). Pubertal development is a multifaceted process influenced by hormonal, genetic, environmental, ethnic, nutritional, and socioeconomic factors, with genetic contributions accounting for approximately 50-80% (2,3).

The Coronavirus disease 2019 (COVID-19) pandemic, one of the most significant global health crises of recent times, highlighted the critical role of environmental factors in pubertal timing (4-6). During this period, restrictions on outdoor activities, increased sedentary behaviors, overnutrition, and excessive screen time were common, all of which have been implicated in early pubertal onset (4-7). Observations and studies during the pandemic lockdown reported a threefold increase in precocious puberty cases compared to prior years (7).

In this study, we aimed to evaluate girls presenting with early or precocious puberty during COVID-19 pandemic and to compare their clinical features with those of girls diagnosed with CPP in the five years before the pandemic.

## MATERIALS AND METHODS

This retrospective study included 36 girls (Group 1) presenting with suspected early puberty during the COVID-19 pandemic

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(March 2020 – July 2021) and 40 girls (Group 2) diagnosed with idiopathic CPP between 2015 and 2019. Demographic, anthropometric, clinical, and laboratory data were obtained retrospectively from the patients' medical records. The local ethics committee approved the study.

Patients with MRI abnormalities of the brain and/or pituitary gland as well as other endocrine diseases or chronic conditions were excluded. The pubertal stages were classified according to the Tanner scale (8). Central precocious puberty in girls was defined by a combination of clinical signs of puberty, including the onset of breast development before the age of 8 years, increased growth velocity, accelerated bone maturation, increased uterine and ovarian volumes, a pubertal basal LH level, and a peak LH level above 5 IU/L following a GnRH stimulation test. The target height was calculated using the formula: [(Father's height in cm - 13) + Mother's height in cm] / 2. Standard deviation scores (SDS) were calculated according to age- and sex-specific national standards (9,10). The Greuclih-Pyle method was used for bone age assessment (11). Birth weight according to gestational age were classified as follows: small for gestational age (SGA) if the birth weight and/or birth length is below -2 SDS, large for gestational age (LGA) if the birth weight and/or birth length was above 2 SDS and appropriate for gestational age (AGA) if within -2 and 2 SDS.

Statistical analyses were conducted using the SPSS statistical software, version 22. Due to non-normal distribution, continuous variables are presented as medians and interquartile ranges (IQR) to indicate central tendency and variability, while categorical variables are summarized as counts and percentages. The non-parametric Mann–Whitney U test was applied to compare the medians, considering the non-normal distribution of the covariates. The chi-square test was conducted to determine whether there was a difference between two or more groups. All tests were performed as two-tailed, with statistical significance established at $p \leq 0.05$.

## RESULTS

In Group 1, 22.2% (n=8) of patients presented in 2020, while 77.8% (n=28) of them presented in 2021. The median age of breast budding onset was 7.7 years (IQR: 1.0, range 5.6–8.5) in Group 1 and 7.4 years (IQR: 1.0, range 4.0–8.0) in Group 2, with a statistically significant difference ($p < 0.001$). Breast development stages were comparable between the groups. In Group 1, 26 patients (72.2%) presented with breast development stage 2, 8 (22.2%) with stage 3, and 2 (5.5%) with stage 4. In Group 2, 21 patients (52.5%) presented with stage 2, 17 (42.5%) with stage 3, and 2 (5%) with stage 4. No significant differences were found between Group 1 and Group 2 regarding the puberty stages (p=0.077).

Among Group 1 patients, four girls, one of them was adopted, presented with menarche (ages between 9.0-10.5 years). In Group 2, four cases presented with menarche (ages between 7.6-9.2 years).

In both Group 1 and Group 2, there was one patient who was born from an In vitro fertilization (IVF) pregnancy. In Group 1, the patient was born as a preterm twin and was AGA, while the patient in Group 2 was born at term but was SGA. In Group 1, 88.9% of the cases (n=32) were born at term, while 11.1% (n=4) were preterm. Among the girls in this group, 86.1% (n=31) were born AGA, 5.6% (n=2) were SGA, and 8.4% (n=3) were LGA. In Group 2, 95% (n=38) of the cases were term, while 5% (n=2) were preterm. The birth weights of the girls in this group were 77.5% (n=31) AGA, 17.5% (n=7) SGA, and 5% (n=2) LGA.

Family history of early puberty among relatives was 13.8% (n=5) in Group 1, while in Group 2, this rate was 5% (n=2). In Group 1, the median maternal age at menarche was 13 years (IQR: 1.38; range: 9.0–15), whereas in Group 2, it was 12 years (IQR: 1.0; range: 10.5–15). The median target height was 161.1 cm (IQR: 8.85; range: 147.6–172) in Group 1, while it was 160.1 cm (IQR: 4.78; range: 152.1–169.7) in Group 2. No statistical difference was found between the groups (p=0.550).

While the demographic details of the groups and their comparison are provided in **Table 1**, the laboratory findings of the groups and the comparison of these findings are shown in **Table 2.** While the basal E2 level was significantly higher in Group 1 (p=0.042), the peak LH and FSH levels during the GnRH stimulation test were significantly higher in Group 2 (p=0.003 and p=0.002, respectively) **(Table 2).**

**Table 1. Demographic data of the groups and their comparison between groups**

| | Group 1 Median (IQR) (Range) | Group 2 Median (IQR) (Range) | p |
|---|---|---|---|
| **CA (years)** | 8.07 (1.37) (6.04;11.7) | 7.89 (1.35) (4.2;9.3) | 0.038 |
| **Height (cm)** | 132.7 (14.3) (115.3;157.1) | 131 (16.8) (103.2;145.1) | 0.250 |
| **Height (SDS)** | 1.12 (1.68) (-1.64; 3.6) | 1.1 (1.82) (-1.6;5.2) | 0.441 |
| **BMI (kg/m$^2$)** | 18.0 (4.6) (12.2;28) | 17.9 (4.45) (13.7;27.5) | 0.835 |
| **BMI (SDS)** | 0.94 (1.76) (-2.8;2.5) | 0.85 (1.41) (-1.4;2.9) | 0.473 |
| **TH (cm)** | 161.1 (8.85) (147.6;172) | 160.1 (4.77) (152.1;169.7) | 0.555 |
| **TH (SDS)** | -0.34 (1.51) (-2.64;1.52) | -0.51 (0.75) (-1.87;1.12) | 0.636 |
| **BA (years)** | 8.83 (2.2) (5.0;12.5) | 8.83 (2.4) (3.5;12.00) | 0.952 |
| **PAH (cm)** | 158.9 (9.2) (147;173.8) | 157.7 (7.95) (140.2;174.8) | 0.122 |
| **PAH (SDS)** | -0.72 (1.56) (-2.74;1.82) | 0.93 (1.35) (-3.9;2.0) | 0.122 |
| **ΔTH-PAH (SDS)** | 0.1 (1.4) (-2.3;2.1) | 0.4 (2.0) (-2.4;3.0) | 0.640 |

IQR: Interquartile range, CA: Chronological age, SDS: Standard deviation score, BMI: Body mass index, TH: Target height, BA: Bone age, PAH: Predicted adult height

**Table 2. Labatory findings of the groups and their comparison between groups**

| | | Group 1 Median (IQR) (Range) | Group 2 Median (IQR) Range | p |
|---|---|---|---|---|
| **Basal LH (mIU/mL)** | | 0.47 (1.82) (0.1; 15.3) | 0.70 (2.0) (0.1; 10.2) | 0.181 |
| **Basal FSH (mIU/mL)** | | 3.6 (2.3) (1.0; 11.66) | 2.2 (2.55) (0.67;9.7) | 0.241 |
| **Basal E2 (pg/mL)** | | 19.2 (33.8) (1.97; 254) | 5.0 (21.4) (5.0;88.8) | 0.042 |
| **Basal DHEAS (mcg/dL)** | | 84.6 (70.4) (5.47; 364) | 76.0 (64.8) (8.9; 160.4) | 0.710 |
| **LHRH test** | **LH peak (mIU/mL)** | 5.38 (4.52) (2.43; 13.7) | 10.7 (15.4) (2.29; 66.4) | 0.003 |
| | **FSH peak (mIU/mL)** | 8.9 (4.52) (5.0; 13.4) | 13.2 (5.15) (5.6; 23.7) | 0.002 |
| | **LH/FSH** | 0.68 (0.27) (0.2; 1.5) | 0.96 (1.01) (0.2; 3.8) | 0.068 |
| **Uterus volume ($mm^3$)** | | 3.3 (2.78) (0.9; 32.6) | 4.9 (5.75) (1.6; 43.4) | 0.019 |
| **R over volume ($mm^3$)** | | 2.5 (1.3) (0.9; 12.9) | 2.4 (2.1) (0.5; 11.2) | 1.000 |
| **L over volume ($mm^3$)** | | 2.5 (1.4) (0.8; 9.1) | 2.7 (2.0) (0.3; 10.7) | 0.760 |

LH: Luteinizing hormone, FSH: Follicle-stimulating hormone, E2: Estradiole, DHEAS: Dehydroepiandrosterone sulfate, LH-RH: Luteinising Hormone Releasing Hormone, R: Right, L: Left

## DISCUSSION

In this study, we evaluated the clinical findings of girls presenting with pubertal complaints, such as breast budding, at a pediatric endocrinology clinic during the COVID-19 pandemic in Türkiye. Additionally, we compared these girls, using both clinical and laboratory findings, to girls who were diagnosed with precocious puberty before the pandemic.

Especially in the preliminary data from Italy, it has been reported that the incidence of precocious puberty increased threefold during the lockdown period compared to the previous year (5). Additionally, according to the experiences of the same team during the COVID-19 pandemic phases (2019-2022), they evaluated consultations for suspected precocious or early puberty in girls and reported a significant increase in the rates of central precocious puberty (7).

In our series, the number of cases presenting between 2020 and 2021 was approximately similar to the total number of patients in the five years before the pandemic. Therefore, we can conclude that there was an increase in the prevalence of CPP during the pandemic period in our cohort. However, cases with conditions that could contribute to CPP, such as cranial pathology, neuromotor delay, and epilepsy, were excluded from Group 2. Only cases that fully met the definition of CPP were included in this group. Thus, the number of cases from previous years was relatively low.

Although Verzani et al. indicated that the consumption of hypercaloric foods and overnutrition could be contributing factors to precocious puberty, no statistical difference in BMI SDS was observed between the groups (5). In another study, from Italy, cases of early puberty during the COVID-19 lockdown and the previous five years were compared, and no difference was observed in the BMI SDS (11). As in previous studies, Oliveira Neto et al. also did not find a statistically significant difference between groups, although they reported that obesity was more common (36.4% versus 18.2%); however, the group sizes were different in their study (12). In our cohort, we also did not find a statistically significant difference in BMI-SDS when comparing cases from the pandemic period with those from the pre-pandemic period.

In our cohort, we found that the median serum E2 levels of patients presenting during the pandemic (Group 1) were higher than those who presented before the pandemic (Group 2) (p=0.042). We observed that the high median estrogen level in Group 1 was related to markedly elevated E2 levels in two cases of patients who presented with menarche at age 9. In previous studies, no significant difference was reported between serum E2 levels (7,12,13).

Interestingly, in our cohort, despite the higher median serum E2 level in Group 1, the median uterine volume was statistically significantly greater in Group 2 (p=0.019). Although no statistical difference was found between the groups, the number of girls with a pubertal stage above stage 2 was higher in Group 2. Moreover, the median LH peak was also higher in Group 2. The advanced pubertal stage and high peak LH levels may be attributed to the higher uterine volumes observed in Group 2.

While Oliveira Neto et al. reported that the mean ovarian volumes were larger in girls who presented before the pandemic (12), we observed no significant difference in the ovarian volumes between the groups (p=1.000 and p=0.760). This discrepancy may be attributed to the small sample size and heterogeneity within the groups in all the studies.

During the pandemic, being forced to stay at home and consequently spending excessive time on electronic devices, whether for educational or recreational activities, may have decreased melatonin levels among children (14). Melatonin secretion is known to be stimulated by darkness and inhibits gonadotropin release (15). Although there was no objective data on screen times for the girls in our cohort during the pandemic, it is reasonable to consider that restrictions during the lockdown period may have contributed to this.

Additionally, the activation of the genes *KISS1* and *KISS1R*, which encode kisspeptin and its receptor, respectively, along with the inactivation of the makorin ring finger 3 (*MKRN3*) gene, play significant roles in the activation of GnRH secretion, leading to the onset of puberty (16-18). Chen et al. reported that when comparing girls who presented during the pandemic with those who presented before the pandemic, MKRN3 levels were lower, and kisspeptin levels were higher in those seen during the pandemic (13). In our study, neither the MKNR3 nor kisspeptin levels of patients who presented during the pandemic period or before the pandemic were available. However, psychological stress, dietary changes, and alterations

in melatonin secretion due to excessive exposure to electronic devices during the pandemic may have led to a decrease in MKRN3 levels and an increase in kisspeptin levels through epigenetic regulation. However, several cohorts are needed to obtain sufficient evidence to explore this topic further.

In conclusion, we present a cohort of girls who presented with central precocious puberty (CPP) during the COVID-19 pandemic and in the 5 years before COVID-19. The number of patients was similar in both groups, however, we observed increasement in CPP presentations during the pandemic. Although high BMI is often cited as a contributing factor, it was not different in our cohort. Additionally, although we lack objective data in this cohort, it is suggested that environmental factors related to pandemic conditions—such as prolonged use of electronic devices and reduced physical activity—may have contributed to epigenetic reprogramming associated with puberty timing, potentially shifting the onset of puberty to an earlier age. However, studies with larger patient populations are needed for more conclusive data.

**Ethics Committee Approval:** This study was approved by the ethics committee of Istanbul Faculty of Medicine Clinical Research Ethics Committee (29/11/2024 - 23)

**Informed Consent:** Written consent was obtained from the participants.

**Peer Review:** Externally peer-reviewed.

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RESEARCH ARTICLE

# Evaluation of Patients with Severe Combined Immunodeficiency Due to Adenosine Deaminase Deficiency: A Single-Center Experience

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## ABSTRACT

**Objective:** This study aimed to evaluate the clinical, immunological, and prognostic features of seven patients diagnosed with Adenosine Deaminase-Deficiency Severe Combined Immunodeficiency (ADA-SCID) at Marmara University. The aim of this study was to enhance the recognition and management of this condition, which is characterized by impaired lymphocyte development and early severe infections.

**Methods:** This retrospective study included seven patients with ADA-SCIDs who were monitored from 2012 to 2024. Patient data, including demographics, clinical findings, laboratory results, and imaging, were retrieved from hospital records. Diagnostic criteria focused on ADA enzyme activity and genetic mutations. Treatment regimens, such as immunoglobulin replacement, antimicrobial prophylaxis, enzyme replacement therapy, and hematopoietic stem cell transplantation (HSCT), were documented. Statistical analyses were performed using descriptive methods.

**Results:** The cohort (6 males, 1 female) presented a median age at diagnosis of 3 months. Consanguinity was observed in 86% of cases. Key symptoms included lymphopenia, recurrent infections, thymus absence, and systemic manifestations. Six patients received HSCT, and two underwent matched donor transplantation. One patient received gene therapy because of the absence of a matched donor. Opportunistic infections were prevalent, including cytomegalovirus and recurrent skin infections noted. Overall, two patients died of post-HSCT complications.

**Conclusions:** ADA-SCID is a life-threatening condition characterized by early severe infections and systemic manifestations. Early diagnosis and tailored treatment, including HSCT and gene therapy, are essential for improving survival outcomes. This study emphasizes the importance of early diagnosis to improve the survival and management outcomes of patients with ADA-SCID.

**Keywords:** Adenosine Deaminase Deficiency, Child, Hematopoietic Stem Cell Transplantation Inborn Errors of Immunity, Lymphopenia, Severe Combined İmmunodeficiency

## INTRODUCTION

Adenosine deaminase (ADA) deficiency is a rare autosomal recessive disorder of purine metabolism [1]. Among patients with ADA deficiency, 80% presented with infantile severe combined immunodeficiency (SCID). Although the global incidence of this disease is unknown, it is estimated to occur in 1 in 200,000 live births [2]. ADA is a critical enzyme that is highly expressed in mammalian tissues, particularly the thymus and lymphoid cells. It converts adenosine (Ado) and deoxyadenosine to inosine and deoxyinosine in purine catabolism. Autosomal recessive defects in ADA lead to toxic accumulation of Ado and dAdo in cells, plasma, and tissues, impairing lymphocyte development and function. Thymic dysplasia and increased T-cell apoptosis are observed in patients with SCID, resulting in SCID symptoms with severe deficiency of T, B, and NK cells [1-3].

Approximately 80% of patients with ADA deficiency present with an early-onset severe combined immunodeficiency (ADA-SCID) phenotype, while 15-20% present with a less severe "delayed" or "late-onset" combined immunodeficiency (ADA-CID) phenotype in older children and adults. Patients with ADA-SCID typically experience recurrent, severe infections in the first months of

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life that, if left untreated, often result in death within 2 years. Cytomegalovirus infections, which can be acquired in utero through breastfeeding or blood transfusions, are of particular concern because these pathogens often cause irreversible organ damage [2]. Some patients with ADA deficiency present with Omenn syndrome, which is characterized by erythroderma, enterocolitis, lymphadenopathy, splenomegaly, and hepatic dysfunction [2]. Most patients with ADA deficiency also have a variety of systemic manifestations, including skeletal, brain, pulmonary, hepatic, and skin manifestations [3, 4]. Patients with ADA-CID deficiency may have fewer lymphoid systemic problems; these patients may have bronchiectasis, liver or bone marrow failure, autoimmune disease, or allergy [2]. Autoimmune manifestations include hypothyroidism and diabetes mellitus, hemolytic anemia, thrombocytopenia and neutropenia, and hepatitis [2].

Due to its high success and survival rates, hematopoietic stem cell transplantation (HSCT) from an HLA-matched sibling donor (MSD) or family donor (MFD) is the preferred treatment option for ADA-SCID patients [2, 3, 5]. Another effective treatment option is ADA gene therapy using autologous hematopoietic stem cells. After the diagnosis of ADA-SCID, ADA enzyme replacement therapy conjugated with polyethylene glycol can be applied as a bridge therapy until the patient undergoes HSCT or gene therapy [2, 5].

Untreated patients with ADA-SCID may experience life-threatening opportunistic infections that can lead to irreversible organ failure and death from the first weeks of life. Early diagnosis and effective treatment management significantly increase the survival rate. Therefore, an early diagnosis and treatment access are crucial for patients with ADA-SCIDs. This study aimed to identify the clinical and laboratory characteristics of patients with SCID due to ADA deficiency to facilitate the recognition of the disease and to elucidate its natural course.

## MATERIALS AND METHODS

Seven patients with ADA-SCID who were diagnosed and followed up at the Department of Pediatric Allergy and Immunology of Marmara University between 2012 and 2024 were included in our study. Demographic characteristics, clinical findings, laboratory results, follow-up time, and disease course of the patients were retrospectively evaluated. Data were obtained from patient records and the hospital's electronic system. This study was approved by the ethics committee of Marmara University (09.2019.511).

ADA enzyme activity (nmol/hr/mg) and deoxyadenosine nucleotide (dAXP) levels (mmol/L, %) were measured in dried blood extracts. ADA deficiency was defined as the absence of enzyme activity (<1%) in dried blood extracts or red blood cells and/or the detection of pathogenic biallelic or compound heterozygous variants in the ADA gene [1, 6].

Complete blood count, antibody responses to vaccine antigens, immunoglobulin levels before immunoglobulin replacement therapy, and immunophenotyping results by flow cytometry were evaluated [7]. The presence of documented viral infections and specific microorganisms growing in the culture were recorded. Radiographic images of the patients were evaluated, and the presence or absence of the thymus was noted.

Immunoglobulin replacement therapy, prophylactic treatments, enzyme replacement therapy, HSCT, and ADA gene therapy were recorded. Donor type, conditioning regimen, and post-HSCT complications were also evaluated.

### Data Analysis

Statistical analyses were conducted using Xls and Jamovi 2.3.26 (The Jamovi Project, Australia) software [8]. Descriptive statistical methods such as median and minimum maximum were used in data analysis.

## RESULTS

### *Patient Characteristics*

The study included seven patients (6 Male, 1 Female), two of Syrian origins, and five of Turkish origins. The median age at diagnosis was 3 months (min-max: 1-14), with a median symptom onset of 1 month (min-max: 1-8) and a diagnostic delay of 2 months (min-max: 0-9 months). Consanguinity was present in six patients (86%), with no reported cases of inborn errors of immunity in the families. The most common presenting symptoms were moniliasis and diarrhea in four patients (57%) and lower respiratory tract infection (LRTI) in three patients (42%). None of the patients had tonsillar tissue. Radiographs showed the absence of the thymus in all patients (Figure 2a). At diagnosis, minor dysmorphic features were noted in P4 and P5 (low-set ears and a hooked nose in P4; coarse facial features in P5), along with hepatomegaly in P4, P5, and P7, and an erythematous eczematous rash in P1, P2, P3, and P7. P2 had multiple vesicular lesions around the right eye and nail dystrophy, while pes equinovarus was seen in P6 (Figure 2b). The detailed clinical features are shown in Table 1 and Figure 1.

### *Infection-related and non-infectious complications*

From diagnosis to HSCT, the most common infection was LRTI in all patients, except for those with P2 and P4. P2 experienced recurrent skin infections. Opportunistic infections were observed in all patients except those at P6 and P7. Cytomegalovirus (CMV) viremia was detected in P1, P2, P3, and P4. HSV-associated conjunctivitis, keratitis, and skin infection were observed in P2. Sepsis by Acinetobacter baumannii was observed in P5. P1, P3, and P6 were vaccinated with attenuated live vaccine strains before diagnosis. P1 received the Bacillus Calmette-Guérin (BCG), oral polio, measles, mumps, rubella (MMR), and varicella vaccines, while P3 and P6 received the BCG vaccine. No vaccine-related complications were observed in any patient.

During the assessment of comorbidities, failure to thrive was observed in P1, P4, P5, and P7; chronic diarrhea in P1, P3, and P7; lymphoproliferation in P5; and bronchiectasis in P3. In addition, developmental delays in neuromotor milestones were

**Table 1. Demographic and clinical features of patients**

| Patient ID | P1 | P2 | P3 | P4 | P5 | P6 | P7 |
|---|---|---|---|---|---|---|---|
| **Age at Presentation (month)** | 14 | 1 | 10 | 2 | 5 | 2 | 3 |
| **Sex** | Female | Male | Male | Male | Male | Male | Male |
| **Ethnicity** | Syrian | Turkish | Turkish | Turkish | Turkish | Turkish | Syrian |
| **Consanguinity** | (+) | (+) | (-) | (+) | (+) | (+) | (+) |
| **Clinical Findings** | | | | | | | |
| **Age at onset (month)** | 1 | 1 | 1 | 2 | 1 | 1 | 1 |
| **Presenting complaint** | Chronic diarrhea<br>Moniliasis<br>Eczema | Skin infection | LRTI<br>Chronic diarrhea<br>Moniliasis | Moniliasis | LRTI | Moniliasis | LRTI<br>Chronic diarrhea |
| **Physical examination** | Absent tonsils<br>FTT<br>BCG scar<br>Eczema | Absent tonsils<br>Eczema<br>Vesicular lesions<br>Nail dystrophy | Absent tonsils<br>BCG scar<br>Eczema | Absent tonsils<br>FTT<br>Atypical face<br>HM | Absent tonsils<br>FTT<br>Atypical face<br>HM | Absent tonsils<br>BCG scar<br>Pes equinovarus | Absent tonsils<br>FTT<br>HM<br>Eczema |
| **Clinical Follow-up** | CMV viremia<br>Pneumonia<br>Chronic diarrhea<br>Developmental delay | CMV viremia<br>HSV keratitis<br>Skin infections | CMV viremia<br>Chronic diarrhea<br>Bronchiectasis | CMV viremia | Brain abscess<br>Hemiplegia<br>LP | Pneumonia<br>Ground-glass opacities | Atrial flutter<br>Hypertension<br>Chronic diarrhea |
| **Treatment** | | | | | | | |
| **ERT** | (-) | (+) | (+) | (+) | (+) | (+) | (+) |
| **HSCT** | (+) | (+) | (+) | (+) | (+) | (-) | (+) |
| **GT** | (-) | (-) | (-) | (-) | (-) | (+) | (-) |
| **Outcome** | Alive | Deceased | Deceased | Alive | Alive | Alive | Alive |
| **Genotype (ADA)** | N/P | c.478+2T>C | c.452C>A, c.704G>A L152M, R235Q | c.245G>A R282Q | c.845G>A R282Q | c.478+2T>C | c.556G>A E186K |

**Abbreviations:** ADA: adenosine deaminase, BCG: Bacillus Calmette–Guérin, CMV: Cytomegalovirus, ERT: Enzyme Replacement Therapy, FTT: Failure to Thrive, GT: Gene Therapy, HCST: Hematopoietic Stem Cell Transplantation, HM: Hepatomegaly, HSV: Herpes Simplex Virus, ID: Identification, LRTI: Lower Respiratory Tract Infection, LP: Lymphoproliferation, N/P: Not Performed, SCID: severe combined immunodeficiency

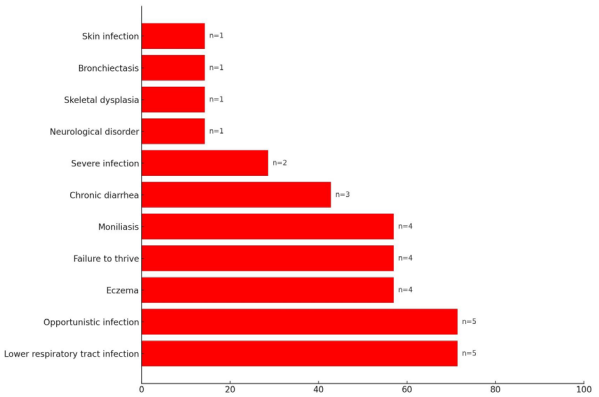


**Figure 1: Distribution of the clinical findings of the patients.**

noted at P1. A brain abscess was found on cranial magnetic resonance imaging (MRI) performed for left hemiplegia in P5. (Figure 2c). Sensorineural hearing loss was not observed in any of the patients. No autoimmune disease or malignancy was observed in any patient. Eczema was observed as an allergic manifestation in 4 patients. The detailed clinical features are shown in Table 1 and Figure 1.

**Laboratory and Imaging Characteristics**

Laboratory tests showed that all patients were lymphopenic at presentation (median, 100/mm$^3$ (min-max: 0-2600). While neutropenia was observed in P4, P6, and P7 (median: 3200/mm$^3$ (min-max: 200-7100), eosinophilia (840/mm$^3$ (min-max: 160-2560) was observed in P1, P2, P4, and P7. The median IgG levels were 369 mg/dL (min-max: 150-1152), IgA 22 mg/dL (min-max: 10-86) and IgM 15 mg/dL (min-max: 0-262). In the immunophenotyping performed by flow cytometry, the T–B–NK– SCID phenotype was identified in all patients, except for P3, who exhibited the T–B–NK+ SCID phenotype. Maternal engraftment was not detected in P6 and P7, for which results are available. ADA enzyme activity was <1% in all patients

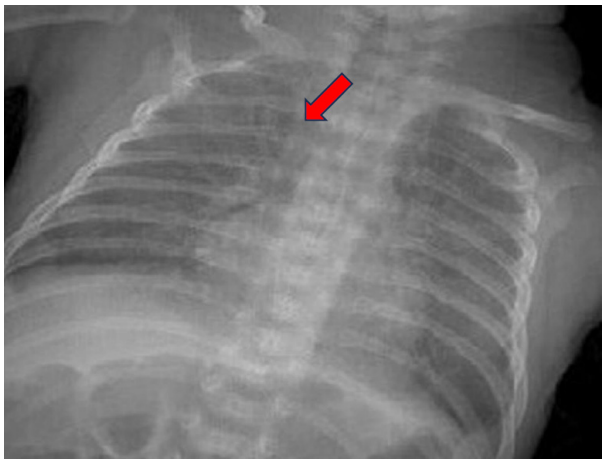

**Figure 2a: X-ray image of P6 showing the absence of the thymus gland.**

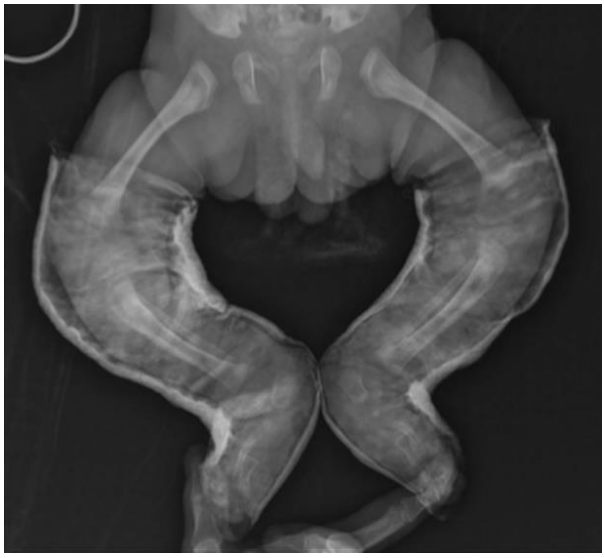

**Figure 2b: X-ray image of P6 illustrating pes equinovarus.**

(except P7, who was not tested) and dAXP levels exceeded 0.1 µmol/mL (or >2% of total) in all cases. The results are summarized in Table 2.

High-resolution computed tomography (HRCT) of the chest was performed at P3, P5, and P6 due to episodes of infection. P3 showed bronchiectasis, pleural thickening, and a tree-in-bud pattern, whereas P5 and P6 showed ground-glass opacities without evidence of bronchiectasis. At P5, a brain abscess was detected on cranial MRI, and subsequent imaging revealed cerebral atrophy. During P3's routine eye examination, MRI and MR angiography were performed on suspicion of papilledema and confirmed dilatation of the vein of Galen.

***Genetic Characteristics***

Five different variants were identified among the six families. Two patients (P2, P6) had a homozygous splice-site mutation, three (P4, P5, P7) had a homozygous missense mutation, and one patient (P3) had a compound heterozygous mutation (Table 1).

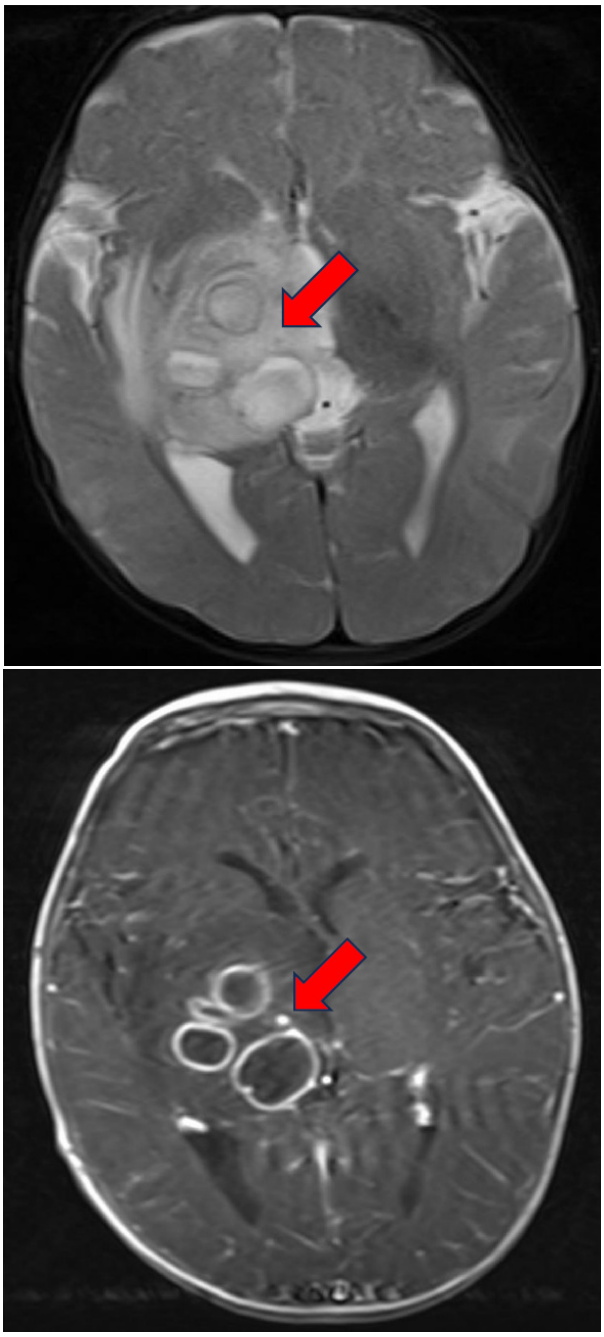

**Figure 2c: Magnetic resonance imaging of P5 showing a brain abscess.**

***Treatments and Outcomes***

All patients received immunoglobulin replacement and pathogen-specific antimicrobial prophylaxis. Six patients received polyethylene glycol conjugated ADA enzyme replacement therapy as bridge therapy for up to two weeks prior to HSCT for a median of 2.5 months (min-max: 1-10). Allogeneic hematopoietic stem cell transplantation (HSCT) was performed in six patients (86%): P1 and P3 received HSCT from a matched sibling donor, P2 and P5 from a matched family (non-sibling) donor, and P4 and P7 from a matched unrelated donor. P6 received autologous hematopoietic stem cell ADA

**Table 2. Laboratory characteristics of the patients at the time of diagnosis**

| Patient ID | P1 | P2 | P3 | P4 | P5 | P6 | P7 |
|---|---|---|---|---|---|---|---|
| White blood cell/mm³ | 5890 | 6400 | 11400 | 2300 (L) | 8700 | 1600 (L) | 2800 (L) |
| ANC/mm³ | 3200 | 3600 | 7100 | 200 (L) | 6500 | 1100 (L) | 1100 (L) |
| ALC/mm³ | 680 (L) | 0 (L) | 2600 (L) | 100 (L) | 100 (L) | 100 (L) | 200 (L) |
| AEC/mm³ | 1370 (H) | 2560 (H) | 300 | 1500 (H) | 200 | 160 | 840 (H) |
| Platelet count/mm³ | 467000 (H) | 524000 (H) | 411000 (H) | 361000 | 426000 (H) | 554000 (H) | 359000 |
| IgG Level (mg/dL) | 1152 | 552 (L) | 369 (L) | 415 | 152 (L) | 275 (L) | 150 (L) |
| IgM Level (mg/dL) | 262 (H) | 17 (L) | 90 | 15 (L) | 5 (L) | 0 (L) | 10 (L) |
| IgA Level (mg/dL) | 86 | 22 | 43 | 22 | 21 | 12 (L) | 10 (L) |
| IgE Level (mg/dL) | 36 | 7 | 121 (H) | 4 (L) | 6 (L) | 0 (L) | 1 (L) |
| CD3+T cells/mm³ | 521 (L) | 34 (L) | 1694 (L) | 5 (L) | 24 (L) | 35 (L) | 13 (L) |
| CD3+4+T cells/mm³ | 250 (L) | 16 (L) | 1166 | 4 (L) | 21 (L) | 24 (L) | 4 (L) |
| CD3+8+T cells/mm³ | 291 (L) | 12 (L) | 396 (L) | 1 (L) | 3 (L) | 7 (L) | 6 (L) |
| CD19+B cells/mm³ | 11 (L) | 4 (L) | 189 (L) | 6 (L) | 0 (L) | 15 (L) | 11 (L) |
| CD16+56+NK cells/mm³ | 105 (L) | 62 (L) | 215 | 30 (L) | 1 (L) | 10 (L) | 49 (L) |
| RTE T cells (%) | 6,8 (L) | - | 9,5(L) | 2 (L) | 0,45 (L) | 1,5 (L) | 0 |
| ADA Activity (nmol/hr/mg) | 0 | 0 | 0 | 0 | 0 | 0 | N/P |
| dAXP levels (%)<br>(µmol/mL) | 11 (H)<br>- | 14 (H)<br>- | 7 (H)<br>- | 48 (H)<br>- | 32 (H)<br>- | -<br>3 (H) | -<br>25 (H) |

**Abbreviations:** ADA: Adenosine Deaminase, AEC: Absolute Eosinophil Count, ALC: Absolute Lymphocyte Count, ALT: Alanine Aminotransferase, ANC: Absolute Neutrophil Count, AST: Aspartate Aminotransferase, dAXP: Deoxyadenosine Nucleotide, H: High, L: Low, Max: Maximum, Min: Minimum, NK: Natural Killer, RTE: Recent Thymic Emigrant.

gene therapy due to the lack of a fully matched donor. Patients were followed for a median of 34 months (min-max: 3-118), and two patients (29%) died due to post-HSCT complications. P2 died due to cranial GVHD after transplantation, but P3's cause of death could not be determined because post-transplantation follow-up was not continued in our clinic.

## DISCUSSION

Severe combined immunodeficiency is a heterogeneous group of disorders caused by genetic defects that impair the development, function, and differentiation of T, B, and sometimes NK cells, resulting in deficiencies in cellular and humoral immune responses. Patients with SCID can be exposed to life-threatening infections in the first months of life [9]. Our ADA-SCID patients had severe infections such as persistent thrush, persistent eczema, recurrent pneumonia, and chronic diarrhea, as well as sepsis and cranial abscess, which typically occur after the first few weeks of life, indicating inborn errors of immunity (IEI). These are the red flags for the diagnosis of ADA-SCID. A history of consanguinity was found in 86% of the ADA-SCID patients. This is a high rate compared to the inbreeding rates reported in the literature [10], and we can say that this result reflects the high inbreeding rate in our region compared to Europe and America. Consanguinity and sibling loss due to IEI are other important indicators of IEI. The referral of patients with both recurrent infections and a history of consanguinity to immunologists should be prioritized [11].

In patients with SCID, opportunistic viral, bacterial, and fungal pathogens and live attenuated vaccines can lead to frequent and life-threatening infections [9,10]. Opportunistic infections were found in most patients (66%). In the Middle East and North Africa (MENA) region, live attenuated vaccines (e.g., BCG), which are widely administered in early infancy, are associated with high mortality rates among patients with IEI [10]. ADA-SCID is usually diagnosed in patients aged 3–12 months, and the median age at diagnosis in our patients was 3 months, which is consistent with the literature [1, 3]. In this context, early diagnosis of patients before live vaccination is critical. The T cell receptor excision circle (TREC) test is a sensitive diagnostic method for the early diagnosis of infants with SCID when used in newborn screening (NBS) [12]. NBS using the TREC test is widely used in the USA and worldwide [13] . However, it has not yet been introduced in Turkey. TREC test should be included in the NBS as soon as possible.

Adenosine deaminase is widely expressed in tissues. Therefore, the effects of ADA deficiency are not limited to the immune system; it also affects numerous organs and systems, including the lungs, liver, kidneys, skeletal system, skin, and nervous system [3, 14]. ADA deficiency is associated with a higher prevalence of non-infectious lung diseases, such as pulmonary alveolar proteinosis (PAP), compared with other genetic forms of SCID [14]. PAP results from surfactant phospholipid and apoprotein accumulation in the alveoli. Patients usually present within the first few weeks of life with respiratory distress, which may be accompanied by hypoxia and dyspnea. Characteristic findings include ground-glass opacities on lung imaging, while histopathologic examination shows granular periodic acid-

Schiff (PAS)-positive lipoprotein material and large, foamy macrophages containing PAS-positive material in the alveoli [2, 14, 15]. Ground glass opacities were observed on HRCT in two patients. One patient underwent bronchoscopy; however, histopathological examination did not reveal PAP. Chronic lung disease is a significant pulmonary problem in patients with ADA deficiency. Approximately 30% of these cases have chronic lung diseases, such as bronchiectasis, bronchiolitis obliterans, interstitial lung disease, and asthma. In our ADA cohort, one patient was found to have bronchiectasis associated with recurrent lung infection [1, 2].

ADA deficiency is characterized by marked skeletal abnormalities. Radiographic changes, such as costochondral cupping and scapular prominence, are observed in 50% of ADA-SCID patients at diagnosis. In patients with suspected congenital immune defects, radiographic findings may indicate ADA deficiency and aid in diagnosis [1, 16, 17]. Although these skeletal abnormalities were not observed, pes equinovarus was noted in one patient.

Individuals with ADA deficiency may experience a range of neurological and behavioral problems, from mild to severe. These include gross and fine motor impairments, seizures, sensorineural hearing loss, speech difficulties, attention deficit, hyperactivity, aggression, and social difficulties. The cognitive abilities of patients with ADA-SCID, as assessed by standardized intelligence tests, have been observed to be lower than those of age-matched controls, and this is thought to be related to increased levels of ADA expression in the brain [2, 14, 15, 18]. In our clinic, we routinely perform eye and hearing evaluations for all patients diagnosed with SCID. No hearing loss cases were observed among the ADA-SCID patient group. However, one patient had neuromotor delay and another had hemiplegia associated with a cranial abscess. Although ADA deficiency can present with various neurological symptoms, other potential neurological disorders should always be considered in the differential diagnosis. When evaluating the involvement of other organs and systems, liver involvement may be observed in individuals with ADA deficiency. Liver dysfunction is usually mild, and severe liver disease is rare [1, 15, 19]. However, abnormal liver function may appear as an early sign in individuals with ADA-SCID and should therefore be carefully evaluated [1]. In our ADA cohort, no clinically significant liver disease was observed although transient mild elevations in transaminase levels were noted in some patients during laboratory analysis. Our patients had skin involvement in the form of diffuse dermatitis, which is also common in other SCID patients. Dermatofibrosarcoma protuberans (DFSP), a rare malignant skin tumor with an increased frequency of ADA enzyme deficiency [1, 15], was not detected in any of our patients.

In patients with ADA-SCID, the initial hematologic finding is typically significant lymphopenia with a T–B–NK– immunophenotype. However, this finding is not specific to the disease, and patients may also present with T–B+NK+ or T–B–NK+ lymphocyte phenotypes [1, 2, 20]. In our study, six ADA-SCID patients exhibited the T–B–NK– SCID phenotype, while one patient exhibited the T–B–NK+ SCID phenotype. Pediatricians must be aware of lymphopenia to refer these patients to immunology clinics early to allow for prompt diagnosis and treatment. Neutropenia is another hematologic abnormality associated with ADA deficiency [1, 2, 14], and it was found in 43% of our patients. T-cell proliferation is either nonexistent or very poor in ADA-SCID patients, and a weak humoral response impairs both antibody synthesis and response to vaccination antigens. In our study, immunoglobulin levels were generally low for age, although two patients had normal IgG levels. ADA-SCID patients may have age-appropriate IgG levels during the first months of life because of maternal transfer via the placenta [1, 2]. In ADA deficiency, ADA enzyme activity is either absent or significantly reduced (<1%), with markedly elevated deoxyadenosine levels in erythrocytes [1-3, 6]. ADA enzyme activity was assessed in six of the patients, none of whom exhibited detectable activity. The deoxyadenosine nucleotide levels were evaluated in all patients and were elevated as expected. The absence of thymus tissue on imaging is a key finding in patients with ADA-SCID, serving as an early indicator of IEI and aiding in the evaluation of infants with suspected ADA-SCID [2]. X-ray imaging was performed in all patients, and none displayed thymus tissue.

HSCT is the preferred curative treatment for ADA-SCID patients. Additionally, ADA gene therapy and ERT are standard treatment options [1, 9, 11, 19]. In our center, the management of ADA-SCID patients begins, as with other SCID patients by ensuring isolation to reduce infection risks. To prevent opportunistic infections, antimicrobial prophylaxis with TMP-SMX, acyclovir, and fluconazole is administered, while antituberculosis prophylaxis with a combination of INH and RIF is initiated for patients who received the BCG vaccine. To prevent CMV infection, breastfeeding is continued if CMV infection is ruled out in the mother. IgRT treatment is started for all patients with SCID, regardless of serum antibody levels. The first step in planning curative treatment involves HLA typing of suitable family members to initiate a bone marrow transplant program, with ADA enzyme replacement as a bridging therapy until definitive treatment is available. Patients who lack suitable families or unrelated donors are directed toward gene therapy [1, 9-11].

In conclusion, untreated patients with ADA-SCID may experience life-threatening opportunistic infections, irreversible organ failure, and death from the first weeks of life. Early diagnosis and effective management can significantly increase the survival rate. Therefore, for the early recognition and treatment of ADA-SCID patients, red flags, including positive family history, early-onset severe or opportunistic infections, severe lymphopenia, and absence of the thymus on chest X-ray, are of great importance.

**Ethics Committee Approval:** This study was approved by the ethics committee of Marmara University (09.2019.511).

**Informed Consent:** Patients were retrospectively evaluated.

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RESEARCH ARTICLE

# Isolation Protocols for Mitigate Influenza in Children

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## ABSTRACT

**Objective:** Influenza, which is characterized by febrile nature and acute respiratory manifestations, poses a significant threat to children with respect to morbidity and mortality. This study aimed to assess influenza infection data among children during periods of enforced isolation and subsequently when these measures were lifted.

**Methods:** This retrospective cross-sectional study categorized patients into two groups: i) influenza direct fluorescent antibody test (DFT) positive patients admitted between June 16, 2021 and June 15, 2022, when isolation measures were in effect (Group 1) and ii) influenza DFT-positive patients admitted between June 16, 2022 and June 15, 2023, when isolation measures were lifted (Group 2).

**Results:** Influenza A was predominant in Group 1, whereas influenza A and B were more evenly distributed in Group 2, demonstrating a statistically significant difference ($p<0.001$). The incidence of moderate-to-severe disease was significantly higher in Group 2 than in Group 1 ($p<0.001$). Groups 1 and 2 differed significantly in terms of hospitalization duration and clinical recovery time (5 [1–7] days vs. 7 [3–9] days, **$P<0.001$ and 3 [1–4] days vs. 5 [4–7] days, $p<0.001$, respectively). The analysis of monthly infection distribution revealed a peak occurring 3 months earlier in Group 2 than in Group 1. In Group 1, compliance rates to vaccination recommendations by physicians and pediatricians were 33% and 58%, respectively, whereas compliance rates in Group 2 were 31.5% and 43.7%, respectively.

**Conclusions:** Implementing basic measures such as hand hygiene and mask-wearing can mitigate viral outbreaks. Elevating the rate of physician-recommended vaccinations can potentially alleviate disease burden and mitigate disease severity.

**Keywords:** Oseltamivir, Influenza, Isolation, Vaccine, SARS-CoV-2

## INTRODUCTION

Influenza is an acute respiratory illness in children that is primarily attributed to influenza A and B viruses. Although it typically manifests as a self-limiting and uncomplicated condition, it cyclically precipitates global epidemics, particularly during the winter months, occasionally leading to morbidity and mortality in children (1). The World Health Organization has underscored the magnitude of seasonal influenza, estimating 1 billion cases annually, with 3–5 million patients experiencing severe disease (2).

Antiviral drugs, particularly oseltamivir, are essential in treating influenza infections. Oseltamivir is recommended because of its ability to reduce symptoms and shorten illness duration in children. It is recommended for serious, complicated, or progressively worsening cases possibly or definitely caused by influenza, irrespective of the influenza vaccination status, with initiation within the first 48 hours of illness (3, 4). The Centers for Disease Control and Prevention Advisory Committee on Immunization Practices and the American Academy of Pediatrics advocate universal annual influenza vaccination for children aged >6 months, barring contraindications preceding the onset of influenza activity in the community (3, 5).

Considering the coronavirus disease 2019 (COVID-19) pandemic that began in 2020, global isolation measures, such as face mask use, hand hygiene, and social distancing, were implemented. In Turkey, schools were closed between September 2021 and

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September 2022 with mandatory mask use and strict isolation measures. September 2022 marked the reopening of schools, the ease of isolation measures, and the start of a return to normalcy. This study examined influenza infection data in children in 2021–2022 when isolation measures were in force and 2022–2023, following relaxation. The primary objective was to assess the impact of lifting isolation measures on influenza infection among children, while the secondary objective was to examine post-pandemic vaccination attitudes.

## MATERIALS AND METHODS

This retrospective cross-sectional study was conducted at a tertiary academic hospital in Istanbul, Turkey, and included patients aged 18 years who were admitted to the pediatric inpatient unit between June 16, 2021 and June 15, 2023. The patient cohort was selected from the hospital's information system using the test entry code for the Influenza Direct Fluorescent Antibody Test (DFT). DFT is an antigen detection method in which viral proteins within infected cells are stained with fluorophore-linked antibodies and visualized under a fluorescence microscope (6). A meta-analysis reported sensitivities of 80.0% for influenza A and 76.8% for influenza B, with a specificity exceeding 98% for the DFT (7).

Patients were categorized into two distinct groups: i) influenza DFT-positive individuals admitted between June 16, 2021, and June 15, 2022, corresponding to the period of isolation measure implementation (Group 1) and ii) influenza DFT-positive individuals admitted between June 16, 2022, and June 15, 2023, subsequent to the easing of isolation measures (Group 2). The selection of the current dates during the comparison of years is attributed to the lifting of measures in June 2022 and the structuring of a school year spanning September to June. Consequently, both years encompassed the influenza season.

In the year of isolation measure implementation, influenza DFTs were submitted by 2540 patients, whereas in the year following the relaxation of isolation measures, 3086 patients submitted influenza DFTs, with a total of 712 patients testing positive for influenza. However, 26 patients were excluded from the study due to missing data. Thus, Group 1 included 292 patients and Group 2 included 394 patients.

The two groups were compared regarding various parameters, including the distribution of admission dates, age (in months), sex, presenting complaints and clinical findings, underlying medical conditions, rate of influenza A/B positivity, incidence of concomitant viral infections, laboratory values, hospitalization rates, treatment status, duration of hospital stay, duration of clinical recovery, rate of moderate to severe disease manifestation, utilization of respiratory support, and vaccination status. The comparison was extended to individuals exhibiting mild and moderate-to-severe disease, with evaluations encompassing age (in months), gender, rate of influenza A/B positivity, underlying medical conditions, and co-infection rates.

Antigen detection using DFT was performed to identify adenovirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and respiratory syncytial virus (RSV). Patients exhibiting significant dyspnea at rest, mental status alterations, clinical deterioration related to hypoxemia, impaired oral intake, and severe complications, such as secondary bacterial pneumonia, as well as those needing mechanical ventilator support were categorized as having moderate to severe disease. The duration of clinical improvement was defined as the period between the initial day of reduced oxygen therapy and the onset of respiratory symptom regression. In Turkey, comprehensive records of citizens' vaccination histories are systematically documented within the national electronic personal health system operated by the Ministry of Health, known as "enabız.gov.tr." This secure platform is accessible to healthcare professionals through a secure login system. The vaccination status of patients was corroborated through two distinct methods: i) verbal declarations provided by parents and ii) cross-referencing with the information available in the national electronic personal health system (enabız.gov.tr). The rate at which physicians recommend vaccines to families was derived from the hospital information notes.

Statistical analysis was conducted using SPSS 15.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The Shapiro–Wilk test was used to determine the normal distribution of variables. Descriptive statistics were employed to present variables, with categorical variables expressed as numbers and percentages and numerical variables presented as mean, standard deviation, median, 25th percentile, and 75th percentile. The chi-square test, Student's t-test, and Mann–Whitney U test were used to compare categorical and numerical variables between the two groups, depending on the sample distribution. Statistical significance was set at $p<0.05$.

## RESULTS

During the period of isolation measures, 305 out of 2540 children (12%) tested positive for influenza, whereas in the year when isolation measures were lifted, 407 out of 3086 children (12.7%) were found to be positive for influenza (p=0.428). The study was conducted on 686 patients (292 in Group 1 and 394 in Group 2) after excluding 26 patients whose data were unavailable. The distribution of patients according to the date of influenza diagnosis is shown in Figure 1. More than half of the patients were male, with a median age of 40 (13–89.75) months. In Group 1, comprising 53.4% males, the median age was 34 (7–83) months, while in Group 2, with 56.6% males, the

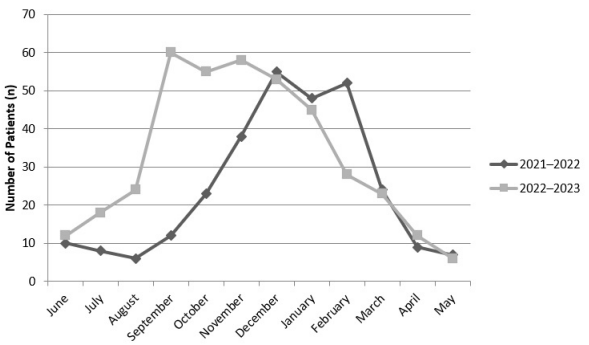


**Figure 1: Influenza infection dates of the patients.**

median age was 44.5 (16–93.2) months (p=0.408 and p=0.004, respectively). Forty patients (5.8%) tested positive for influenza A and B viruses. Table 1 presents data on patient complaints, examination findings, comorbidities, co-infections, laboratory values, hospitalization status, and respiratory support.

Comparison of Group 1 and Group 2 regarding the duration of hospitalization and clinical recovery time revealed a statistically significant difference (5 [1–7] days vs. 7 [3–9] days, p<0.001 and 3 [1–4] days vs. 5 [4–7] days, p<0.001, respectively).

Group 1 included 267 (91.4%) cases of mild disease and 25 (8.5%) cases of moderate to severe disease, whereas Group 2 included 314 (79.7%) mild and 80 (20.3%) moderate to severe cases, indicating a statistically significant difference (p<0.001). Of all patients, only one fatality occurred (in Group 2). The

**Table 1. Patients' complaints, examination findings, comorbidities, co-infections, laboratory values, hospitalization status, treatment, and respiratory support**

| | | Total n (%) | Group 1 n (%) | Group 2 n (%) | p ¶ |
|---|---|---|---|---|---|
| **Influenza A** | | 546 (79.6) | 287 (98.2) | 259 (65.7) | **<0.001** |
| **Influenza B** | | 180 (26.2) | 17 (5.8) | 163 (41.4) | **<0.001** |
| **Complaints** | Fever | 492 (71.7) | 185 (63.4) | 307 (77.9) | **<0.001** |
| | Cough | 327 (47.7) | 151 (51.7) | 176 (44.7) | 0.073 |
| | Nasal discharge | 85 (12.4) | 36 (12.3) | 49 (12.5) | 0.956 |
| | Sore throat | 80 (11.7) | 25 (8.6) | 55 (14.0) | **0.029** |
| | Vomiting | 75 (10.9) | 25 (8.6) | 50 (12.7) | 0.085 |
| | Weakness/Myalgia | 67 (9.8) | 6 (2.1) | 61 (15.5) | **<0.001** |
| | Seizure | 54 (7.9) | 34 (11.6) | 20 (5.1) | **0.002** |
| | Diarrhea | 30 (4.4) | 8 (2.7) | 22 (5.6) | 0.071 |
| | Headache | 16 (2.3) | 4 (1.4) | 12 (3.1) | 0.163 |
| | Mental status changes | 5 (0.7) | 2 (0.7) | 3 (0.8) | 1.000 |
| **Respiratory Finding** | Wheezing | 106 (15.5) | 75 (25.7) | 31 (7.9) | **<0.001** |
| | Dyspnea | 49 (7.1) | 31 (10.7) | 18 (4.6) | **0.002** |
| | Ral and/or Ronkus | 108 (15.7) | 78 (26.7) | 30 (7.7) | **<0.001** |
| | Prolonged expiratory phase | 21 (3.0) | 8 (2.7) | 13 (3.3) | 0.670 |
| | Tachypnea | 5 (0.7) | 0 (0.0) | 5 (1.3) | 0.075 |
| **Underlying Disease** | Prematurity | 9 (1.3) | 5 (1.7) | 4 (1.0) | 0.505 |
| | Congenital heart disease | 11 (1.6) | 6 (2.1) | 5 (1.3) | 0.542 |
| | Neuromotor retardation | 11 (1.6) | 6 (2.1) | 5 (1.3) | 0.541 |
| | Diabetes Mellitus | 4 (0.6) | 3 (1.0) | 1 (0.3) | 0.317 |
| | Bronchopulmonary dysplasia | 3 (0.4) | 2 (0.7) | 1 (0.3) | 0.578 |
| **Co-infection** | Adenovirus | 24 (3.5) | 3 (1.0) | 21 (5.3) | **0.002** |
| | RSV† | 25 (3.6) | 4 (1.4) | 21 (5.3) | **0.007** |
| | SARS-CoV-2‡ | 7 (1.0) | 5 (1.7) | 2 (0.5) | 0.120 |
| **Hospitalization** | No | 585 (85.2) | 128 (43.8) | 134 (34.0) | **0.009** |
| | Yes | 101 (14.7) | 164 (56.2) | 260 (66.0) | |
| **Oseltamivir Treatment** | No | 310 (45.2) | 103 (35.3) | 207 (52.5) | **<0.001** |
| | Yes | 376 (54.8) | 189 (64.7) | 187 (47.5) | |
| **Respiratory Support** | Room air | 576 (84.0) | 238 (81.5) | 338 (85.8) | 0.129 |
| | Oxygen support | 103 (15.0) | 50 (17.1) | 53 (13.5) | 0.192 |
| | NIV§ | 6 (0.8) | 4 (1.4) | 2 (0.5) | 0.213 |
| | MV‖ | 1 (0.1) | 0 (0.0) | 1 (0.3) | 0.349 |
| **Laboratory Values** | Leukocyte ($10^3$/uL) | 9.5±4.3 | 9.7±4.2 | 9.1±4.4 | 0.259* |
| | Neutrophil ($10^3$/uL) | 4.4 (2.8-6.9) | 4.4 (3.0-7.0) | 4.3 (2.6-6.7) | 0.418** |
| | Lymphocyte ($10^3$/uL) | 2.7 (1.5-4.6) | 2.7 (1.5-4.5) | 2.6 (1.5-4.8) | 0.959** |
| | Platelet ($10^3$/uL) | 293±126 | 296±118 | 289±135 | 0.364* |
| | Albumin (g/L) | 44±4.1 | 44.7±3.5 | 43.5±4.3 | **<0.001*** |
| | Procalcitonin (ug/L) | 4.4 (4.1-4.82) | 3.9 (0.11-4.8) | 4.4 (4.1-4.9) | 0.214** |
| | CRP†† (mg/L) | 9.2 (3.5-10.8) | 6.4 (1.7-19.1) | 9.5 (9-10.1) | **0.001**** |
| | Fibrinogen (g/L) | 2.85±1.36 | 1.75±0.82 | 3.49±1.19 | **<0.001*** |

All laboratory values are presented as mean ± standard deviation or median ($25^{th}$–$75^{th}$ percentile).
¶Chi-square test, *Student's t-test, **Mann–Whitney U test
†RSV: respiratory syncytial virus; ‡SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; §NIV: non-invasive mechanical ventilation; ‖MV: invasive mechanical ventilation; ††CRP: C-reactive protein

median age was 42 (15–94) months among those with mild disease and 24 (7–64) months among those with moderate to severe disease, indicating a statistically significant difference ($p<0.001$). The comparison of mild and moderate-to-severe cases is detailed in Table 2.

Figure 2 illustrates vaccine recommendations and the proportion of vaccinated patients. In Group 1, compliance with vaccine recommendations from family physicians and pediatricians was 33% and 58%, respectively. In Group 2, the rates decreased to 31.5% and 43.7%, respectively. Notably, none of the vaccinated patients experienced moderate to severe disease, with all vaccinated patients falling into the mild disease category. However, data on the timing of influenza vaccination and the duration until admission were unavailable.

**Table 2. Comparison of mild-to-moderate-severe disease**

| | | Mild Disease n (%) | Moderate-Severe Disease n (%) | p[¶] |
|---|---|---|---|---|
| **Sex** | **Boy** | 331 (55.6) | 48 (52.7) | 0.606 |
| | **Girl** | 264 (44.4) | 43 (47.3) | |
| **Influenza A** | | 467 (78.5) | 79 (87.8) | 0.040 |
| **Influenza B** | | 159 (26.7) | 21 (23.3) | 0.493 |
| **Group 1 (n=292)** | | 267 (91.4) | 25 (8.5) | **<0.001** |
| **Group 2 (n=394)** | | 314 (79.7) | 80 (20.3) | **<0.001** |
| **Underlying Disease** | Prematurity | 2 (0.3) | 7 (7.9) | **<0.001** |
| | Congenital heart disease | 5 (0.8) | 6 (6.6) | **<0.001** |
| | Neuromotor retardation | 7 (1.2) | 4 (4.4) | 0.024 |
| | Diabetes Mellitus | 3 (0.5) | 1 (1.1) | 0.483 |
| | Bronchopulmonary dysplasia | 1 (0.2) | 2 (2.2) | **0.009** |
| **Co-infection** | Adenovirus | 9 (1.5) | 15 (16.5) | **<0.001** |
| | RSV[†] | 11 (1.8) | 14 (15.4) | **<0.001** |
| | SARS-CoV-2[‡] | 1 (0.2) | 6 (6.6) | **<0.001** |

[¶]Chi-square test
[†]RSV: respiratory syncytial virus; [‡]SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

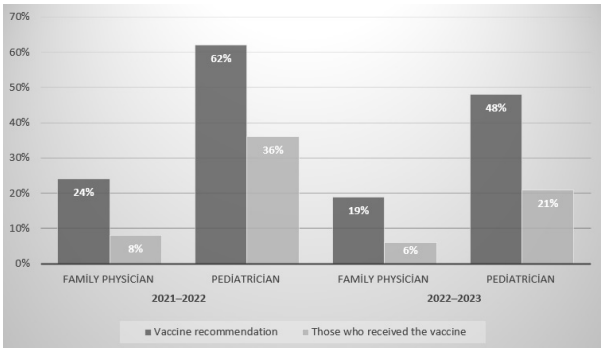


**Figure 2: Vaccine recommendations for patients and families.**

## DISCUSSION

The primary finding of our study was that, following the relaxation of isolation measures, influenza severity increased, whereas the proportion of other viral infections, such as Adenovirus and RSV, increased. Furthermore, a decrease in physicians' recommendations for vaccination and diminished compliance among families were noted in the aftermath of the COVID-19 pandemic.

A notable increase in the mean age of patients diagnosed with influenza was observed in Group 2. The overall mean age was consistent with the findings of a comprehensive 20-year study (8). The observed age-group difference in Group 2 might be attributed to heightened transmission associated with the reopening of schools. Additionally, previous studies have indicated that the average age is higher among patients diagnosed with influenza B than among those diagnosed with influenza A (8). Thus, age differences may have occurred in Group 2, where the incidence of influenza B was higher.

Our study revealed a noteworthy shift in the timing of the influenza peak, which occurred 3 months earlier, accompanied by an overall increase in patient numbers throughout the year following the removal of isolation measures. This deviation from the previous year is attributed to school closures, mask use, adherence to hand hygiene, and reduced time spent in enclosed and crowded environments in the previous year. The abrupt decline in patient numbers from February onward, subsequent to the peak in the year when isolation measures were lifted, can be ascribed to the earthquake that affected a substantial part of the country on February 6, 2023. During this period, a hospital ward was reserved for earthquake victims, reducing hospital admissions. In addition, schools were closed for a month during this period. While a 20-year study indicated that influenza A typically constituted 80% of cases, with influenza B predominating in 5 out of 20 years (8), our study found influenza A to be predominant in both years, with an increase in influenza B cases in the year when isolation

measures were lifted. Furthermore, influenza A exhibits peak transmission 24–48 hours post-illness, whereas influenza B features two peaks, one before and one after illness (9). Hence, in the year when isolation measures were lifted, the surge in patient numbers and the earlier peak may be attributed to these factors.

Consistent with other studies, the prevalent symptoms in our study included fever, cough, and nasal discharge (10, 11). Seizures were observed in 7.9% of patients, a finding similar to that of a 5-year study with a large patient cohort (12). The higher seizure rate in Group 1 may be associated with delayed hospital presentations due to the curfew that year. Additionally, a previous study suggested a close relationship between influenza A and seizure frequency (8). Myalgia was more frequently observed in Group 2, and we suggest that this discrepancy may have arisen from the higher propensity of influenza B to induce myalgia, as evidenced by previous studies (13), coupled with a higher incidence of influenza B cases within Group 2. The higher frequency of respiratory symptoms in Group 1 may be attributed to influenza A predominance (14).

Post-isolation measures, RSV, and adenovirus incidence exhibited a statistically significant increase compared to the previous year. Our data appear to align with a previous study reporting a reduction in viral infections during the COVID-19 pandemic (15). A study published in the United States at the end of 2023, a rise in the prevalence of other viral agents was documented (16). Although not statistically significant, the incidence of scabies, also transmitted by contact, increased in the year isolation measures. This underscores the broader role of preventive measures, such as hand hygiene and mask use, in preventing the spread of various viral infections through close contact, which extend beyond the confines of the COVID-19 outbreak.

In the year following the removal of isolation measures, the number of moderate-to-severe cases was higher, as evidenced by elevated acute-phase reactants, such as C-reactive protein and fibrinogen, increased hospitalization rates, increased oseltamivir initiation rates, and longer durations of hospitalization and clinical recovery. Nearly half of the hospitalized patients in this study had no underlying cause (17). The co-infection rate in the group with a more severe disease course was significantly higher than that in the other group, potentially contributing to disease severity. The severity of the disease may progress more markedly in the presence of co-infections with other viral agents (18, 19). Additionally, during the COVID-19 pandemic, outpatient follow-ups were necessary for some patients due to hospitalization constraints. Consequently, physicians may have opted for broader indications for hospitalization in the following year. This may explain the prolonged duration of hospitalization in these patients. A previous study showed that patients admitted with influenza B infection had longer hospitalization durations than those with influenza A (8). The higher rate of influenza B in Group 2 may have also contributed to the longer hospital stay. Symptoms may be less severe in children who develop influenza despite influenza vaccination (11). Thus, the disparity in vaccination rates between the groups may also have contributed to the differing disease severity. The prevalence of underlying disease and co-infection was significantly higher in the group with more severe disease. Underlying diseases, including co-infections, may exacerbate the severity of influenza (20). Consequently, children with a history of premature birth, congenital heart disease, and lung diseases, such as bronchopulmonary dysplasia, should be approached with heightened caution.

The American Academy of Pediatrics and the Centers for Disease Control and Prevention advocate for the use of oseltamivir as a treatment for influenza in children (1, 20). Studies have shown that oseltamivir is associated with a reduction in the duration of illness by more than 1 day (4, 21). Owing to the retrospective nature of our study, an assessment of the duration of illness in patients starting oseltamivir treatment was unfeasible because the exact date of symptom onset and treatment initiation could not be determined. The increased frequency of oseltamivir use in Group 2 may be attributed to the higher incidence of moderate-to-severe disease in this group and evolving medical practices. Larger-scale prospective studies are warranted to comprehensively explore this topic.

Our study revealed a decline in the rate of vaccination recommendations by family physicians and pediatricians post-pandemic, accompanied by a reduction in the adherence rate among families. The Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention and the American Academy of Pediatrics advocate for universal annual influenza vaccination among individuals aged ≥6 months (3, 5). It is recommended that vaccination be administered before the onset of influenza activity in the community (3, 5). Considering that the post-pandemic influenza peak in our study occurred 3 months earlier than in the previous year, some families may have declined vaccination on the grounds that their children had already acquired influenza. Nevertheless, evidence suggests that both influenza A and influenza B can co-circulate in the same year (8). Therefore, increasing vaccine recommendation rates has the potential to mitigate the impact of influenza epidemics.

Our data closely align with the Weekly Influenza Surveillance data published by the Ministry of Health, suggesting that they accurately depict the influenza trends in Turkey (22, 23).

**Limitations**

Our study has several limitations. The retrospective, single-center design introduces inherent biases and limits the generalizability of the findings. Crucial information, such as the incidence of acute otitis media, the most prevalent complication of influenza, and the date of initiation of oseltamivir treatment, remains undisclosed due to data unavailability. Furthermore, the reasons underlying families' decisions to abstain from vaccination were not elucidated, representing a significant data gap. Although general isolation precautions were observed, the study's efficacy may have

been compromised due to insufficient clarification regarding individual hand hygiene practices and adherence to isolation protocols. Additionally, the absence of the pre-pandemic period in the study design could have affected the statistical power. Fluctuations in the periodicity and annual impact of influenza outbreaks may have also diminished the accuracy of the study; however, given that our study was cross-sectional in nature, establishing a causal relationship was not feasible. Another constraint concerns the inability to distinguish between the subtypes of influenza A, which could have provided nuanced insights into its epidemiological dynamics. These limitations underscore the need for cautious interpretation of our findings and highlight avenues for improvement.

## CONCLUSIONS

The prevention of viral outbreaks can be effectively achieved through the adoption of simple yet impactful measures, including meticulous hand hygiene practices and the consistent use of face masks. Mitigating disease burden and alleviating disease severity necessitates concerted efforts to enhance vaccination rates. This can be accomplished by encouraging increased vaccination recommendations from family physicians and pediatricians. Moreover, the implementation of vaccination programs, supported by government initiatives, plays a pivotal role in achieving widespread immunization coverage, thereby contributing to the overall reduction of disease prevalence and severity within the population.

**Ethics Committee Approval:** This study was approved by the ethics committee of the Clinical Research Ethics Committee of the Health Sciences University, Haseki Training and Research Hospital, decision number 62/2023.

**Informed Consent:** Written consent was obtained from the participants.

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RESEARCH ARTICLE

# Parental Awareness of Microplastic Pollution and its Relation with Healthy Living Education Consciousness

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## ABSTRACT

**Objective:** This study was conducted to determine the relationship between parents' awareness of microplastic pollution and their levels of awareness regarding their children's physical health, nutrition, hygiene, mental health, and social activity.

**Methods:** This study was conducted based on the correlational survey model. The study group consisted of parents residing in different cities of Turkey who had at least one child aged between 0 and 18 years during the research period. A total of 362 parents participated in the study. Data were collected from February to May 2023 using the "Personal Information Form," "Microplastic Pollution Awareness Scale," and "Parental Healthy Living Education Consciousness Level" scales. Descriptive statistics [number, percentage, mean, standard deviation, median (25th-75th percentile)], Mann-Whitney U, Kruskal-Wallis H tests, and Spearman correlation analysis were used in the evaluation of the data.

**Results:** The average age of the participating parents was found to be 39.0±7.1, 53.9% were male, 92.8% were married, 67.2% had an education level of an associate degree or higher, and 47.2% had two children. Women's physical health, nutrition, hygiene, and mental health scores were statistically significantly higher than those of men, and it was determined that the parents participating in this study had a high awareness of microplastic pollution. The nutrition and mental health scores of parents with education levels of high school or lower were found to be statistically significantly lower than those with an associate degree or higher. Weak positive linear relationships were found between physical health and awareness of microplastic pollution (r=0.142; p=0.007).

**Conclusions:** In line with the results of the study, educational programs can be developed for parents, especially fathers, to help their children develop healthy eating and hygiene habits, and awareness levels of families regarding physical and mental health can be increased. Informative trainings can be created and disseminated to encourage mothers and fathers to equally share responsibilities by addressing gender roles in society.

**Keywords:** Child, Parent, Awareness, Microplastics, Healthy Living

## INTRODUCTION

Plastics and synthetic organic polymers have become ubiquitous in daily life over the past 75 years, with global production surpassing 367 million tons in 2020. Despite its versatile uses and benefits, plastic accumulation is predicted to triple by 2050, however, concerns have been raised about its environmental impact (1). Plastics are attractive in industry and commerce because of their low weight, durability, flexibility, low cost of production, easy availability, and mass production (2). They are valued for their affordability, light weight, and durability. However, their resistance to corrosion and decomposition poses a significant environmental challenge, reducing their practicality (3). The waste generated from plastic production and consumption poses serious risks to both the environment and public health (4). With the influence of environmental factors, these plastic wastes spread over vast areas and gradually break down into smaller particles, forming microplastics (5).

Microplastics are substances frequently detected in water, soil, and atmospheric environments and pose a serious threat to environmental safety and human health (6). Microplastics, defined as particles smaller than 5 mm, are emerging pollutants primarily originating from plastics. Evidence of microplastics in the environment dates back to the 1970s (7). Today, industries like pharmaceuticals and cosmetics incorporate microplastics into many daily products, leading to environmental pollution through wastewater (8, 9). Microplaastics are found in surface waters (10), beaches (11), food products such as salt and honey (12), bottled waters, on land, and in the air (13). The small size, challenges in detection, and potential to cause adverse effects

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make them a significant concern for the environment, animals, and human health (14).

Exposure to microplastics through ingestion, inhalation, and skin contact can occur via products, food items, and airborne particles, leading to oxidative stress, inflammation, and toxicity in biological systems. This may result in chronic inflammation and increased risk of neoplasia. In addition, microplastics can release absorbed pollutants and pathogenic organisms (15, 16, 17).

Since 1948, the World Health Organization has defined health as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity." (18). In today's societal conditions, families bear a significant and heavy responsibility. Parents have important tasks and responsibilities in the physical, motor, cognitive, social, and emotional development of their children, as well as their physical and mental health and education. Parents' understanding of child development significantly influences their approach to raising children. For instance, research has shown that mothers who communicate positively with their children typically possess greater knowledge of child development than those who do not (19).Knowledge of child development involves understanding the typical behaviors expected from a child at a given stage. This allows the assessment of the child's capabilities and setting reasonable expectations for their behavior (20). Accessing health services, safeguarding children from physical harm (e.g., emphasizing seat belt and helmet use), and possessing knowledge about health and safety, including promoting hygiene and nutrition, are vital aspects of parenting (21).

Upon reviewing the relevant literature, no study has simultaneously addressed and evaluated the healthy lifestyle education awareness levels of parents and their knowledge levels about microplastic pollution. The aim of this study was to determine the relationship between parents' awareness of their children's physical and mental health, nutrition, hygiene, mental health/social activity, and awareness of microplastic pollution.

## MATERIALS AND METHODS

### Research design

This study was conducted using the relational scanning model. Scanning models represent a research approach that aims to describe a situation in detail, either in the past or in the current state. In the relational scanning model, the event, individual, or object that is the subject of the research is defined within its unique conditions. In line with this objective, detailed descriptions of both situations are first made in terms of specific variables, and then these descriptions are compared based on common criteria (22)

### Study group

The study group consisted of parents living in different cities of Turkey who had at least one child between the ages of 0 and 18 years during the research period. A total of 362 parents participated in the study. Data were collected between February and May 2023.

### Data collection and implementation tools

In this study, data collection forms were created using Google Forms. Participants were informed that participation was voluntary and that they were free to participate or not. Participants who agreed to participate answered the questions in approximately 10-15 minutes. The data were collected over approximately 4 weeks. Participants were able to choose the most suitable time to answer the questions and provided more honest answers because their identities were not disclosed. .In this study, the "Personal Information Form," "Microplastic Pollution Awareness Scale," and "Parental Healthy Living Education Consciousness Level" scales prepared by the researchers were used.

#### *Personal information form*

The "Personal Information Form," prepared by the researchers includes questions about the parents' ages, educational backgrounds, occupations, and income statuses, as well as the number and ages of their children.

#### *Microplastic Pollution Awareness Scale (MPAS)*

The Microplastic Pollution Awareness Scale is a scale developed to measure individuals' awareness of microplastic pollution (23).[17] Exploratory Factor Analysis (EFA) was applied to the data obtained from the application of the scale to 586 participants, revealing that the scale has a 3-factor structure and that the factors explain 49.57% of the total variance. Confirmatory Factor Analysis (CFA) was then conducted to confirm the obtained factor structure. The overall reliability coefficient of the scale was 81%. The Microplastic Pollution Awareness Scale is a Likert-type scale and consists of 14 items, including 5 negative and 9 positive items. The maximum score that can be obtained from the scale is 28, and the score obtained from the scale is directly proportional to the individual's level of awareness of microplastic pollution. There are 3 factors. Factor 1: Awareness of preventing microplastic pollution; Factor 2: Awareness of the effects of microplastic pollution on organisms; Factor 3: Awareness of the effects of microplastic pollution on human health. In this study, the total Cronbach's α coefficient for the Microplastic Pollution Awareness Scale was calculated as 0.885, for Factor 1 as 0.805, for Factor 2 as 0.748, and for Factor 3 as 0.758.

#### *Parental Healthy Living Education Consciousness Level (PHLECL)*

In the initial stage, a draft scale with 47 items was prepared for the Parental Healthy Living Education Consciousness Level Scale, and after obtaining expert opinions, a draft form with 40 items was created (24). To test the comprehensibility of the draft scale, a face-to-face interview survey was conducted with 30 parents, and the reliability of the scale was determined to be 92% based on the analysis of the responses obtained. The 40-item scale was then applied to 390 individuals; however, 10 items that violated the reliability and validity according to confirmatory factor analysis and other statistical methods were excluded. Consequently, a four-factor scale consisting of 30 items was developed. These factors are, respectively, named "Physical Health, Nutrition, Hygiene, and Mental Health/Social Activity."

When examining the Cronbach's alpha reliability coefficients, it is observed that these coefficients are calculated as 0.808 for the "Physical Health" factor, 0.758 for the "Nutrition" factor, 0.846 for the "Hygiene" factor, and 0.903 for the "Mental Health/Social Activity" factor. Accordingly, it can be concluded that all factors have high reliability. The Cronbach's alpha reliability coefficient for the 30 items on the scale was calculated as 0.9485, indicating that the scale is highly reliable. In this study, it was found that the Cronbach's alpha coefficients for the total score and subscales of the scale were 0.96, 0.85, 0.88, 0.93, and 0.96, respectively.

**Data analysis**

For the analysis of the data obtained from this study, the SPSS (Statistical Package for Social Sciences) for Windows 26 (SPSS Inc., Chicago, IL, USA) software package was used. The assumption of normal distribution of quantitative variables was checked using the Kolmogorov-Smirnov test. Descriptive statistics for quantitative variables with normal distribution were presented as mean ± standard deviation, whereas for quantitative variables not showing normal distribution, median (25th-75th percentile) was used. Descriptive statistics for categorical variables are presented as frequency and percentage. Mann–Whitney U and Kruskal-Wallis H tests were used to compare scale scores among independent groups. The relationships between variables were examined using Spearman's correlation analysis. A significance level of $p < 0.05$ was considered statistically significant.

**Ethical aspects of the Study:** Permission dated 10.11.2022 and numbered 42161/76 was obtained from the Kayseri University Non-Interventional Clinical Research Ethics Committee.

**RESULTS**

This section discusses the sociodemographic characteristics of the participants, comparisons of scale scores based on various variables, and relationships between the scales.

When examining Table 1, the minimum and maximum values of the scores obtained from the Parental Healthy Living Education Consciousness Level and Microplastic Pollution Awareness Scales, as well as the mean and standard deviation scores, are provided.

The average age of the parents participating in the study was found to be 39.0 ± 7.1, with 53.9% being male, 92.8% being married, 47.2% having two children, 67.2% having their own education level, and 63.5% having their spouse's education level at the associate's degree or bachelor's degree (Table 2).

Parental Healthy Living Education Consciousness Level Scale and Microplastic Pollution Awareness Scale scores were compared in female and male participants (Table 3). There was a statistically significant difference between females and males in physical, nutrition, hygiene, and mental health scores. Female scores in physical health, nutrition, hygiene, and mental health were statistically significantly higher than those of males (p=0.008; p=0.001; p=0.017; p=0.032). There were no statistically significant differences between genders in MPAS total, factor 1, factor 2, and factor 3 scores (p>0.05).

The comparison results of the Parental Healthy Living Education Consciousness Level Awareness Level Scale and Microplastic Pollution Awareness Scale scores according to marital status are presented in Table 4. We found a statistically significant difference between married and single individuals in terms of nutrition and hygiene scores. The scores for nutrition and hygiene were statistically significantly higher for married individuals than for singles (p=0.038; p=0.033). No statistically significant difference was determined between married and single individuals in terms of physical and mental health, MPAS total score, factor 1, factor 2, and factor 3 scores (p>0.05). Considering that the highest score obtained from the MPAS is 28, it was observed that the awareness of the parents participating in this study regarding microplastic pollution was high.

Parental Healthy Living Education Consciousness Level Scale and Microplastic Pollution Awareness Scale scores were compared according to the participants' education levels (Table 5). The analysis revealed no statistically significant difference

**Table 1. Minimum and Maximum Scores, Arithmetic Means, and Standard Deviations of Parental Healthy Living Education Consciousness Level Scale and Microplastic Pollution Awareness Scale scores**

| Scales | n | Minimum | Maximum | | Standard Deviation |
|---|---|---|---|---|---|
| **PHLECL** | | | | | |
| Physical Health | 362 | 7 | 35 | 27,64 | 5,28 |
| Nutrition | 362 | 4 | 20 | 16,53 | 3,35 |
| Hygiene | 362 | 6 | 30 | 26,18 | 4,89 |
| Mental Health | 362 | 13 | 65 | 55,52 | 9,87 |
| **MPAS** | | | | | |
| MPAS Total | 362 | 7 | 28 | 22.52 | 4,95 |
| Factor 1 | 362 | 2 | 10 | 8,69 | 1,85 |
| Factor 2 | 362 | 2 | 10 | 8,03 | 1,94 |
| Factor 3 | 362 | 0 | 8 | 5,78 | 1,94 |

in physical health, nutrition, hygiene, mental health, MPAS total score, factor 1, factor 2, and factor 3 scores based on educational status (p>0.05).

Parental Healthy Living Education Consciousness Level Scale and Microplastic Pollution Awareness Scale scores were compared according to the spouse's education level (Table 6). A statistically significant difference was observed in the nutritional and mental health scores based on spouse's educational status. The nutrition and mental health scores of individuals whose spouse had a secondary education were significantly lower than those with an associate degree, undergraduate, or postgraduate education (p < 0.05).

Results of correlation analysis between the scores of the Parental Healthy Living Education Consciousness Level and Microplastic Pollution Awareness Scale and the age and number of children are presented in Table 7. There was a weak negative linear relationship between age and nutrition (r=-0.150; p=0.05) and mental health (r=-0.200; p<0.01).

The correlation analysis results between the scores of the Parental Healthy Living Education Consciousness Level Scale and the Microplastic Awareness Scale are presented in Table 8. A weak linear relationship was found between physical health and the total score of the Microplastic Pollution Awareness Scale (r=0.142; p<0,05), factor 2 (r=0.141; p<0,05) and factor 3 (r=0.125; p<0.05).

**Table 2. Sociodemographic Characteristics of Participants**

| Sociodemographic Characteristics | n (%) |
|---|---|
| **Age (±SS)** | 39,0±7,1 |
| **Gender** | |
| Female | 167 (46,1) |
| Male | 195 (53,9) |
| **Marital Status** | |
| Married | 336 (92,8) |
| Single | 26 (7,2) |
| **Education Level** | |
| Secondary Education or below | 52 (14,4) |
| College or bachelor's degree | 238 (65,7) |
| Master's or PhD | 72 (19,9) |
| **Couple Education Level** | |
| Secondary Education or below | 84 (23,2) |
| College or bachelor's degree | 230 (63,5) |
| Master's or PhD | 48 (13,3) |
| **Children Number** | |
| 1 Child | 140 (38,7) |
| 2 Children | 171 (47,2) |
| 3 children or older | 51 (14,1) |

n: frequency; %: Percentage, $\bar{X}$: Mean, SS: standard deviation.

**Table 4. Comparison of scale scores according to marital status**

| | Marital Status | | | |
|---|---|---|---|---|
| | **Married** | **Single** | **Z** | **p** |
| **PHLECL** | | | | |
| Physical Health | 28 (25 - 31) | 29 (20,8 - 33) | -0,053 | 0,958 |
| Nutrition | 17 (15 - 19) | 16,5 (10,8 – 18,5) | -2,075 | **0,038** |
| Hygiene | 28 (24 - 30) | 25,5 (17,8 – 29,3) | -2,127 | **0,033** |
| Mental Health | 58 (52 - 63) | 57,5 (38,5 – 64,3) | -0818 | 0,413 |
| **MPAS** | | | | |
| MPAS Total | 24 (19 - 27) | 21,5 (16,8 - 26) | -1,200 | 0,230 |
| Factor 1 | 10 (8 - 10) | 9 (6 - 10) | -1,536 | 0,124 |
| Factor 2 | 9 (6,3 - 10) | 7,5 (6 - 10) | -0,962 | 0,336 |
| Factor 3 | 6 (4 - 8) | 6 (4 - 7) | -0,905 | 0,366 |

Z: Mann–Whitney U test statistical descriptive statistics are presented as median (25th - 75th percentile).

**Table 3. Comparison of Scale Scores by Gender**

| | Gender | | | |
|---|---|---|---|---|
| | **Female** | **Male** | **Z** | **p** |
| **PHLECL** | | | | |
| Physical Health | 29 (26 - 32) | 28 (24 - 31) | -2,644 | **0,008** |
| Nutrition | 18 (16 - 20) | 17 (14 - 19) | -3,253 | **0,001** |
| Hygiene | 29 (25 - 30) | 27 (24 - 30) | -2,378 | **0,017** |
| Mental Health | 59 (53 - 63) | 56 (51 - 63) | -2,141 | **0,032** |
| **MPAS** | | | | |
| MPAS Total | 24 (18 - 26) | 24 (19 - 27) | -0,596 | 0,551 |
| Factor 1 | 10 (8 - 10) | 10 (8 - 10) | -0,210 | 0,834 |
| Factor 2 | 8 (6 - 10) | 9 (6 - 10) | -1,269 | 0,204 |
| Factor 3 | 6 (4 - 8) | 6 (4 - 8) | -0,237 | 0,813 |

*Z: Mann–Whitney U test statistical descriptive statistics are presented as median (25th - 75th percentile).*

**Table 5. Comparison of scale scores by education level**

| | Education Level | | | | |
|---|---|---|---|---|---|
| | Secondary education or below | College or bachelor's degree | Master's or PhD | H | p |
| **PHLECL** | | | | | |
| Physical Health | 27 (22,3 - 32) | 28 (25 - 31) | 29 (27 - 32) | 3,139 | 0,208 |
| Nutrition | 16 (12,3 - 19) | 17 (15 - 19) | 18 (15,3 - 19) | 4,048 | 0,132 |
| Hygiene | 28 (22 - 30) | 28 (24 - 30) | 28 (26 - 30) | 1,439 | 0,487 |
| Mental Health | 57,5 (17,3 - 62) | 58,5 (51 - 64) | 57 (53 - 62) | 2,602 | 0,272 |
| **MPAS** | | | | | |
| MPAS Total | 24,5 (17,3 - 26) | 24 (19 - 27) | 24 (19 - 27) | 0,833 | 0,659 |
| Factor 1 | 10 (7 - 10) | 10 (8 - 10) | 9 (8 - 10) | 0,674 | 0,714 |
| Factor 2 | 9 (6 - 10) | 9 (6 - 10) | 8 (7 - 10) | 0,623 | 0,732 |
| Factor 3 | 6 (4 - 7) | 6 (4 - 8) | 6 (4 - 8) | 0,306 | 0,858 |

*H: Kruskal-Wallis H Test Statistic*
*Descriptive statistics are presented as median (25th - 75th percentile).*

**Table 6. Comparison of scale scores according to spouse educational status**

| | Spouse's Educational Status | | | | |
|---|---|---|---|---|---|
| | Secondary education or below | College or bachelor's degree | Master's or PhD | H | p |
| **PHLECL** | | | | | |
| Physical Health | 27 (23 - 31) | 28 (26 - 31) | 29 (26,3 – 32,8) | 4,860 | 0,088 |
| Nutrition | 16 (12 -18,8)[a] | 17 (15 - 19)[b] | 18 (16 - 20)[b] | 12,244 | **0,002** |
| Hygiene | 28 (22 - 30) | 28 (24 - 30) | 29 (26 - 30) | 4,843 | 0,089 |
| Mental Health | 55,5 (48,3 - 63)[a] | 59 (52 - 63)[b] | 60 (53 - 64)[b] | 6,567 | **0,037** |
| **MPAS** | | | | | |
| MPAS Total | 24 (18 - 26) | 24 (18 - 27) | 24,5 (22 - 27) | 0,362 | 0,597 |
| Factor 1 | 10 (8 - 10) | 10 (8 - 10) | 10 (8 - 10) | 0,916 | 0,633 |
| Factor 2 | 8,5 (6 - 10) | 8 (6,8 - 10) | 9 (7 - 10) | 0,733 | 0,693 |
| Factor 3 | 6 (4 - 8) | 6 (4 - 8) | 6,5 (5 – 7,8) | 1,035 | 0,596 |

H: Kruskal-Wallis H Test Statistic
Descriptive statistics are presented as median (25th - 75th percentile).
Similar letters within the same row indicate statistical similarity, whereas different letters indicate statistical differences.

**Table 7. Spearman correlation coefficients of age, number of children, and scale scores**

| PHLECL | Age | Children Number |
|---|---|---|
| Physical Health | -0,088 | -0,045 |
| Nutrition | **-0,150*** | -0,079 |
| Hygiene | -0,080 | 0,018 |
| Mental Health | **-0,200**** | -0,092 |
| **MPAS Total** | **0,032** | **0,024** |
| Factor 1 | -0,024 | 0,066 |
| Factor 2 | 0,024 | 0,024 |
| Factor 3 | 0,056 | 0,026 |

*p<0,05, **p<0,01

**Table 8. Spearman's correlation coefficient between scale scores**

| | Physical Health | Nutrition | Hygiene | Mental Health |
|---|---|---|---|---|
| **MPAS Total** | 0,142* | 0,123 | 0,087 | 0,094 |
| **Factor 1** | 0,046 | 0,019 | 0,027 | 0,033 |
| **Factor 2** | 0,141* | 0,121 | 0,087 | 0,097 |
| **Factor 3** | 0,125* | 0,121 | 0,076 | 0,073 |

**p<0,05*

## DISCUSSION AND CONCLUSION

The study investigated the relationship between parents' awareness levels of their children's physical health, nutrition, hygiene, mental health/social activity, and microplastic pollution. The frequency and type of plastic material use in our daily lives can be noticeable. Plastic materials are used in almost every place, such as homes, workplaces, and streets. Knowledge regarding microplastic toxicity remains limited and largely depends on exposure concentration, particle characteristics, absorbed pollutants, involved tissues, and individual sensitivity, requiring further research (15). Various studies have indicated the potential for metabolic disorders, neurotoxicity, and increased cancer risk in humans. Additionally, microplastics can release both adsorbed substances on their surfaces and their component compounds (13). Some diseases can be caused by social factors such as poverty (malnutrition), dietary habits (high sugar, fat) and behaviors (alcoholism). The social disadvantages mentioned above can lead to conditions

such as diabetes (25), chronic liver disease (26), and chronic kidney disease (27). Similarly, in the case of microplastics, various social factors such as inhalation and skin exposure routes, poverty (housing and hygiene), occupation (working in synthetic textile factories), and personal behavior (use of cosmetics containing microplastics) can influence and determine microplastic exposure (13). In this study, it was observed that parents had an average score of 22.5 points on the microplastic pollution awareness scale. The highest possible score was 28. The parents who participated in this study had a high awareness of microplastic pollution. When reviewing the relevant literature, it was found that there had been no research conducted specifically with parents on this topic, but studies had been conducted with students and adults. For example, a study conducted in India (28) observed that women showed more awareness than men and were also more willing to adopt pro-environmental practices. Educational qualification and the field of education also had a significant and directly proportional impact on the level of awareness. Despite adequate awareness of plastic pollution, awareness specific to microplastics was limited. In another study on this topic, it was stated that while most participants demonstrated a good level of awareness regarding plastic waste, about half of them heard the word "microplastic" for the first time (29). Another study conducted in China showed that only 74% of the participants had heard of microplastics for the first time (30). In this study, mothers were found to have statistically significantly higher scores in physical health, nutrition, hygiene, and mental health than fathers. The nutrition and hygiene scores of married parents were also statistically significantly higher than those of singles. As primary caregivers at home, parents can play a vital role in improving the child's health outcomes if they possess appropriate knowledge, information, and resources. Parental education can directly and indirectly affect children's health through various channels. This research indicates that women have statistically significantly higher physical, nutritional, hygiene, and mental health. These results emphasize the potential effects of gender on health and lifestyle factors. Regarding family health, the role of the mother is critical. Mothers take care of the health needs of her children. Additionally, she is responsible for aspects related to nutrition, hygiene, and health requirements. Traditionally, mothers have been seen as the primary providers of food to children because they are often the primary caregivers (31, 32). The mother is obligated to raise healthy infants and children, as she determines their health and illness. A previous study has shown that key factors influencing family health are the mother's education level, age, and economic status, as well as her knowledge and attitudes regarding preventive measures and disease treatment (33). In our society, it is commonly observed that men are generally assigned the role of father, leader, and breadwinner, while women are often given the roles of mother and homemaker (34). These gender differences can be addressed in a context in which society assigns different social roles and expectations to women and men. It is conceivable that women often carry more responsibility within the family and therefore may focus more on healthy lifestyle habits. The nutrition and mental health scores of individuals whose spouses had an education level of secondary education or below were significantly lower than those with spouses who had an associate, undergraduate, or postgraduate degree. We found weak positive linear relationships between physical health and awareness of microplastic pollution. The argument is emphasized that educated parents can more effectively shape the health outcomes of their children. Firstly, despite using the same resources and time, these learners can use them more effectively than less educated parents. For example, seeking medical services at appropriate times, adopting preventive care practices, practicing better hygiene, making healthy dietary choices, timely vaccination, paying attention to birth spacing, and utilizing prenatal/postnatal and neonatal care services that support the child's health. Second, being generally educated enables individuals to enter better-paying jobs and provides them with more comprehensive health insurance opportunities for their families. Third, educated individuals tend to have stronger social networks, effective communication skills, personal control, and healthy behaviors. They also have a lower future discount rate, thereby increasing the likelihood of investing in family health care in the future (35). The parents who participated in this study had high awareness of microplastic pollution. Mothers exhibited higher levels of awareness regarding the physical, nutritional, hygiene, and mental health of their children compared to fathers. A weak positive relationship was found between parents' awareness of physical health and microplastic pollution. Considering the limited number of studies conducted on this topic and the results of this study, educational programs could be developed for parents, especially fathers, to promote healthy nutrition and hygiene habits in their children. Additionally, efforts could be made to increase awareness among families about physical and mental health issues. Encouraging equal sharing of responsibilities between mothers and fathers in line with gender roles can be promoted. Although there is no single correct approach to parenting, finding common ground within the framework of scientific approaches and conditions that prioritize the child's highest benefit undoubtedly leads to positive outcomes for the child's physical and mental health.

The limitations of the current study must be acknowledged when interpreting and applying the findings derived from the study's content. The study's scope is confined to the data collected from the sample group and research instruments. The parents involved in the study constitute the investigated population. It is recommended to conduct studies using different samples and educational interventions as part of the research.

**Ethics Committee Approval:** This study was approved by Clinical Research Ethics Committee of Kayseri University (42161 – 10.11.2022)

**Informed Consent:** Written consent was obtained from the participants.

**Peer Review:** Externally peer-reviewed.

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

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RESEARCH ARTICLE

# Evaluation of the Clinical Phenotype and Follow-up of Children with 'Non-sustained' Ventricular Tachycardia Detected on 24-hour Rhythm Holter

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## ABSTRACT

**Objective:** Non-sustained ventricular tachycardia (NSVT) is an important arrhythmic finding in pediatric patients, with varying clinical implications based on the presence of structural heart disease. This study aimed to evaluate the clinical characteristics, follow-up, and management of children diagnosed with NSVT detected on 24-hour Holter monitoring.

**Methods:** A retrospective analysis was conducted on 22 pediatric patients (9 males, 13 females) aged 2.5–17 years, who were diagnosed with NSVT between 2015 and 2023. Patients with sustained VT, channelopathies, or electrolyte-related prolonged QTc were excluded. Echocardiography, electrocardiography, and Holter monitoring were performed for all patients. Statistical analyses were conducted using SPSS 26.0, with significance set at $p<0.05$.

**Results:** Monomorphic NSVT was observed in 14 patients (64%), while polymorphic NSVT was found in 8 patients (36%). The mean VT rate was 161.2±18.7 bpm, with polymorphic VT demonstrating a significantly higher rate (175.3±4.4 bpm) than monomorphic VT (153.3±4.6 bpm) ($p=0.003$). The prematurity index was significantly lower in polymorphic VT (0.75±0.03) than in monomorphic VT (1.1±0.03) ($p<0.001$). Additionally, QTc was longer in polymorphic VT (463.5±5.1 ms vs. 425.4±6.5 ms, $p=0.004$). Structural heart disease was present in 50% of cases, with polymorphic VT being predominantly associated with cardiomyopathies (dilated, hypertrophic, and non-compaction). Only three patients (14%) were symptomatic, and all symptomatic patients had structural heart disease. All patients with underlying cardiac abnormalities were treated with beta-blockers, primarily propranolol, while those with normal echocardiography were followed without medication. No adverse effects, syncope, or mortality were observed during follow-up.

**Conclusion:** NSVT in pediatric patients should be carefully evaluated, particularly in the presence of structural heart disease. While monomorphic NSVT in structurally normal hearts appears benign, polymorphic NSVT is strongly associated with cardiomyopathies, necessitating medical therapy and close monitoring. Individualized management based on echocardiographic findings and arrhythmic characteristics is essential for optimizing patient outcomes.

**Keywords:** Non-sustained ventricular tachycardia, Holter monitoring, beta-blockers

## INTRODUCTION

Ventricular tachycardia (VT) is an arrhythmia that arises from the working ventricular myocardium (1). When a child presents with wide QRS complex tachyarrhythmia, it is always important to first consider the diagnosis of VT. We know that children present with late-related aberrancy associated with supraventricular tachycardia, but VT accounts for an estimated 80% of all wide complex rhythms across all ages (2). Most children with clinically significant ventricular arrhythmias have structural or functional cardiac disease. However, pediatric patients with chronic ventricular arrhythmias without organic heart disease or other predisposing factors are also being identified today (3).

It is important to determine the characteristics and clinical findings of ventricular tachycardia because the follow-up and treatment indications of ventricular tachycardia that develops in patients with structurally normal hearts and in the presence of underlying organic heart disease may vary depending on these criteria.

## MATERIALS AND METHODS

In our retrospective study, 22 (9 boy, 13 girl) patients aged between 2.5 and 17 years were evaluated. Patients with non-sustained VT detected on 24-hour rhythm holter during follow-up in the pediatric cardiology department between 2015 and 2023 were included. All patients underwent echocardiographic and electrocardiographic evaluation during follow-up.

Each patient underwent ambulatory ECG recording. A Schiller medico AR was used to record a 3-channel ECG. For all episodes of VT, the following values were measured by manual analysis of the rhythm strips: average rate and consecutive number of

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episodes, heart rate prior to episode, the R-R interval before the episode, QT interval of the preceding sinus rhythm, and coupling interval (R-R'). The prematurity index of the initiating beat of VT was defined as (R-R')/QT.

Each patient had at least one 24-hour rhythm Holter recording containing episodes of non-sustained VT. Ventricular tachycardia should be diagnosed whenever three or more QRS complexes, which have a morphology different from that of the normal QRS complexes, occur at a rate greater than 120 beats/rain or 25% greater than the average normal sinus rate. Non-sustained VT is a ventricular tachycardia that lasts less than 30 seconds and terminates spontaneously.

Patients with sustained VT detected on 24-hour Rhythm Holter recording, patients with channelopathies such as long QT syndrome, arrhythmogenic right ventricular dysplasia (ARVD), Brugada syndrome, and patients with prolonged QTc values due to electrolyte disorders were excluded from the study.

**Statistical Analysis**

Statistical analysis of patient data was performed using SPSS (Statistical Package for Social Sciences) Windows 26.0 software. Kolmogorov-Smirnov test was applied to evaluate the suitability of the data for normal distribution. Normally distributed continuous variables are expressed as mean ± standard deviation (SD); Continuous variables that do not show normal distribution are presented as median and interquartile range (IQR). Categorical data are reported as frequencies (n) and percentages (%). In comparing the differences between groups, the independent-groups t-test was used for normally distributed data and Mann–Whitney U test was used for non-normally distributed data. The relationships between categorical variables were analyzed using the Pearson's chi-square test. The statistical significance level was set as $p<0.05$.

**RESULTS**

In our study, 22 patients (9 male %41,13 female %59) with non-sustained VT detected on 24-hour Rhythm Holter were included. The average age of the patients was 11,65±4,3 (min:2.5, max:17 years).

The number of beats of each episode ranged from 4 to 53 beats, and the average number of beats was 15,2±14. The rate of VT was 161,2±18,7 beats/min and ranged from 126 to 195 beats/min. The rate of VT was 153,3±4,6 in monomorphic VT group and it was 175,3±4,4 in polymorphic VT group; there was no statistically significant difference between them.

Heart rate before VT was 85,9±13,6 beats/min (range, 55 to 122 beats/min). In the monomorphic VT group it was 86,8±1,8 beats/min, and in the polymorphic VT group, the heart rate before VT was 84,4±7,6 beats/min. There was no significant difference between groups, and the majority of episodes were observed at a normal heart rate.

Monomorphic non-sustained ventricular tachycardia (VT) was detected in 14 of the 22 patients included in the study, and polymorphic non-sustained VT was observed in the remaining 8 patients. The average age of monomorphic and polymorphic VT patients was 11,5±1,1 and it was 11,9±1,7 for polymorphic VT patients.

The prematurity index was 0,98±0,2, in patients with polymorphic VT it was (0,75±0,03) significantly smaller than (1,1±0,03) in patients with monomorphic VT. Additionally, the number of beats (29,1±5,2) in patients with polymorphic VT was significantly higher than (7,2±1) in patients with monomorphic VT.

Polymorphic VT was detected in only 1 of 11 patients with normal echocardiography, whereas monomorphic VT was detected in 10 of these patients with a structurally normal heart. In other words, 10 of 11 patients with normal echocardiography had monomorphic VT. Four patients; 1 Operated ASD,1 operated DORV, 1 operated Fallot tetralogy

| VARIABLES | TOTAL (n=22) | MONOMORPHIC VT (n=14) | POLYMORPHIC VT (n=8) | P value |
|---|---|---|---|---|
| Age | 11,65±4,3 | 11,5±1,1 | 11,9±1,7 | 0,66 |
| Male gender (n, %) | 9, (%41) | 6, (%42) | 3, (%37) | 0,8 |
| Number of beats | 15,2±14 | 7,2±1 | 29,1±5,2 | <0,001 |
| Heart rate before VT | 85,9±13,6 | 86,8±1,8 | 84,4±7,6 | 0,76 |
| Rate of VT | 161,2±18,7 | 153,3±4,6 | 175,3±4,4 | 0,003 |
| The coupling interval (msn) | 665,6±151,4 | 728,7±37 | 555,3±37,6 | 0,008 |
| QTc (msn) | 439,2±28,1 | 425,4±6,5 | 463,5±5,1 | 0,004 |
| Prematurity index (CI/RR) | 0,98±0,2 | 1,1±0,03 | 0,75±0,03 | <0,001 |
| RR Interval(msn) | 716,9±131,3 | 695,4±15,8 | 754,6±73 | 0,73 |
| Symtom (n, %) | 3 | 0 | 3, (%37) | 0,014 |
| Syncope | 0 | 0 | 0 | |
| Mortality | 0 | 0 | 0 | |
| Follow-up period (age) | 3,3±1,8 | 2,8±0,4 | 4,2±0,7 | 0,11 |

VT: Ventricular tachycardia

and 1 patient with mitral valve prolapse had monomorphic VT. However, polymorphic VT was observed in all patients with cardiomyopathy (2 dilated cardiomyopathy, 2 hypertrophic cardiomyopathy, 2 non-compaction cardiomyopathy, 6 patients in total) and in 1 patient with a mass within the mitral papillary muscle. In summary, only one of the 8 patients with polymorphic VT in our study had a structurally normal heart.

Only 2 of the patients with non-sustained VT detected in Rhythm Holter had palpitations. One of these two patients had noncompaction cardiomyopathy and the other had dilated cardiomyopathy. The patient, who was followed up for a mass within the papillary muscle, could not describe any symptoms because he was young (2.5 years old), but he did complain of crying. The remaining patients were asymptomatic.

In our study, medical treatment was given to all patients with underlying structural heart disease for non-sustained ventricular tachycardia attacks, even if they were asymptomatic. Beta blockers are the first choice for medical treatment in our clinic. The most frequently used drugs in this group are propranolol and metoprolol. In our study, for treating 6 patients with cardiomyopathy; Only 1 patient with dilated cardiomyopathy was treated with metoprolol, and the other 5 patients were treated with propranolol. Propranolol was also used for the treatment of 1 patient with a mass within the mitral papillary muscle. No drug side effects were observed in patients who received medical treatment. Non-sustained VT detected by rhythm Holter in all asymptomatic patients without underlying heart disease was monitored clinically, and no drug treatment was given.There were no syncopes or deaths among the patients we followed.

**DISCUSSION**

Many researchers have found that unifocal ventricular extrasystoles seen in asymptomatic children with a structurally normal heart (4-6).

In a study conducted in children, sudden death, syncope, and ventricular tachycardia were not observed in patients with polymorphic PVCs and couplets and in those with a normal heart determined by echocardiography and cardiac catheterization during the 2.5-year follow-up period (6).

In an adult study by Yusuf et al., the relationship between heart rate in sinus rhythm and prematurity index and VT rate was examined. They demonstrated a significant inverse correlation between the prematurity index and ventricular arrhythmia rate. In this study, they also found that the incidence of couplets and triplets was higher in patients with ventricular tachycardia (75% and 50%, respectively) than in patients without ventricular tachycardia (43% and 25%), this was not statistically significant (7).

Infants with incessant or frequent paroxysmal ventricular tachycardia have a high risk of myocardial tumors (8, 9). In our study, one patient with a mass within the mitral papillary muscle had polymorphic non-sustainable VT episodes on 24-hour rhythm testing. This patient was under follow-up for 6 months, and after non-sustained VT episodes were detected, beta blocker treatment was started because of an underlying cardiac mass. In the literature, if arrhythmias are resistant to drug treatment in the presence of cardiac mass, surgical treatment is recommended. Our patient remained under medical monitoring because the arrhythmia was controlled with medication, and no increase in mass size was observed.

In many patients who are thought to have a structurally normal heart, if there is a life-threatening arrhythmia, an echo must be performed because sometimes the first clinical symptom in diseases such as cardiomyopathy or myocarditis may be arrhythmia (6, 10-12).

In almost all studies, patients with symptomatic arrhythmias had an underlying cause, whereas those with non-sustained, asymptomatic ventricular tachycardia often had normal hearts. It has been reported in the literature that cases with sudden death at long-term follow-up are patients with underlying cardiac pathology. In children, PVCs and VT occur mostly because of ventricular reentry and with underlying structural cardiac pathology (cardiomyopathies, cardiac mass, previous cardiac surgery), the presence of dilatation in the heart chambers or surgical scar due to the operation causes the arrhythmias to be resistant (5,10,11,13,14).It has also been observed that ventricular arrhythmias resolve spontaneously over time in some patients with structurally completely normal hearts (8).

All patients with symptomatic ventricular arrhythmia should be treated. The first choice of treatment in the literature is beta blockers (8).Studies show that non-sustained VTs seen in asymptomatic patients with normal hearts have a benign prognosis. For this reason, although the treatment options and exercise restriction issues are controversial, existing information does not remain valid (15, 16). The recommended follow-up method for symptomatic children with non-sustained ventricular tachycardia is ventricular couplets. Children with ventricular couplets and simple or multiform PVCs should have 24-hour Rhythm Holter and should be followed regularly by a pediatric cardiologist even if they have a structurally normal heart (17, 18). This is how we monitor ventricular couplets and non-sustained VTs at our clinic.

It is important to pay attention to the presenting symptoms and complexity of the arrhythmia when deciding on non-sustained VT and PVC management and treatment.

Cardiomyopathies, cardiac surgery, and heart tumors are also risk factors for VT. Because the heart is not normal in these situations, medical therapy or surgery for tumors may be necessary (4).

**CONCLUSIONS**

Patients with non-sustained VT detected in childhood should be evaluated by considering many factors. Each patient should be carefully evaluated with a detailed evaluation of the presence of underlying structural heart disease and ventricular tachycardia, and the treatment method and follow-up should be determined.

**Ethics Committee Approval:** This study was approved by the İstanbul Faculty of Medicine Clinical Research Ethics Committee (18/10/2024 - 20)

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CASE REPORT

# Attention Attention; Anaphylaxis After Skin Testing with Aeroallergens

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## ABSTRACT

Skin prick tests (SPT) are widely used in the diagnosis of allergic diseases because of their reliability, simplicity, cost-effectiveness, and rapid results. Herein, we report a 4-year-old boy who developed anaphylaxis with aeroallergen SPT in an asthmatic child. SPTs were positive for both house dust and Plantago allergens.Although the frequency of systemic reactions to SPTs is low, these tests should only be performed in medical facilities with appropriate equipment and well-trained medical personnel for anaphylaxis.

**Keywords:** Anaphylaxis, skin prick test, aeroallergen, asthma

## INTRODUCTION

Allergen skin prick tests (SPTs) are considered the test of choice and commonly used for the diagnosis of allergic diseases because of their reliability, simplicity, cost-effectiveness, insignificant invasiveness, and rapid results (1). SPTs allow the evaluation of the sensitization status to a wide spectrum of allergens, including aeroallergen, foods, drugs, latex, and venoms. Local reactions, such as localized skin symptoms, urticaria, angioedema, and oral pruritus, may occasionally occur (2). There are case reports of systemic allergic reactions to SPT, but these reactions are extremely rare in large case series. Systemic reactions reported in previous studies of SPTs are also uncommon, and anaphylaxis has been reported even less frequently, ranging from 0.015% to 0.4% (3-6). Aeroallergens were in the minority of allergens causing adverse reactions during skin prick testing, with food allergens, venoms, and antibiotics being the most commonly reported (4,7-8).

In this report, we described a case of anaphylaxis in a patient diagnosed with asthma and allergic rhinitis after undergoing SPT with aeroallergen. The parents provided informed consent for the publication of this case report.

## CASE

A 4-year-old male patient was treated at our pediatric allergy clinic with a medical history of frequent inhaler use during the winter for the past 2 years. Three months ago, the patient was prescribed fluticasone propionate inhaler therapy, and since then, he has used it twice (125 mcg daily). His most recent asthma exacerbation occurred 3 months ago, after which he continued to use his inhaler regularly as prescribed. In addition, the patient experienced recurring nasal symptoms, including congestion, itching, and frequent sneezing. The patient also reported 2 urticaria episodes triggered by cocoa and strawberries a year ago. In addition, the patient's father had a history of asthma.

Laboratory tests revealed an eosinophil count of 400/mm3 (3.5%) with normal serum IgA, IgG, and IgM levels for his age and an elevated total serum IgE level of 1740 IU/mL. The basal serum tryptase level was 4.09 mg/L (normal <11.4 ng/mL).

On the day of admission to the SPT, the physical examination of the patient was normal. He had no recent infection, asthma attack, or intake of NSAIDs that could facilitate anaphylaxis.

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The selected area was cleaned with alcohol, allergen extracts, a positive control (histamine dichloride concentration of 10 g/L), and a negative control (glycerin saline at the same concentration). Tests were performed on the volar side of the forearm at least 2–3 cm from the wrist and antecubital fossa. One drop of each test solution was placed on the skin 2 cm apart in the same order for each subject. A lancet is used to puncture the epithelial layer of the skin without bleeding. The largest wheal and flare diameters were recorded 15 min after application. A result with a maximum wheal diameter of at least 3 mm and at least 3 mm larger than the negative control was considered positive. (9,10).

However, he experienced an adverse reaction within 10 minutes following the skin prick test with common aeroallergen, including house dust mites, grass, tree pollen, molds, latex, and animal dander (ALK-Abelló group, Ukraine). The patient complained of abdominal pain and subsequent vomiting. During his clinical examination, mild abdominal tenderness was noted, and angioedema developed around his eyes within 20 minutes. No rash was observed on his skin. Anaphylaxis was considered, and 0.01 mg/kg adrenaline was administered intramuscularly. Additionally, oral cetirizine (0.5 mg/kg) and intravenous methylprednisolone (1 mg/kg) were administered. During close follow-up, the vital signs were observed to be within normal limits. His abdominal pain and nausea rapidly regressed within 10 minutes after intramuscular adrenaline administration, and his angioedema regressed within 2 hours. His skin prick tests revealed positivity for both house dust allergens [ *Dermatophagoides pteronyssinus (Der p 1)* and *Dermatophagoides farinae (Der p 2*)] and for Plantago, with flare and wheal reactions of 30x30 mm, 4x8 mm and 4x6 mm, respectively. Histamine was 5x10 mm, the negative control was 0 mm, and the other pollens (grass, weeds, and tree pollens), animal dander, and mold were negative. The patient was prescribed an adrenaline autoinjector, and his family received training for its use.

During the 3-month follow-up 3 months after the event, laboratory evaluation was performed using the CAP system to confirm the positivity of the skin prick test: *Der p1* sIgE >100 kU/L, *Der p 2* sIgE >100 kU/L, grass sIg E <0.1 kU/L, cat dander sIg E <0.1 kU/L, dog dander sIg E <0.1 kU/L.

**DISCUSSION**

There are several reports on systemic reactions after SPTs. In a study conducted in the United Kingdom, the results of 31000 SPTs, including both children and adults, were evaluated, and a total of 24 systemic reactions (6 cases <16 years old) were reported, with a systemic reaction rate to SPT of 0.077% (4). Food allergens were reported to be responsible for 75% (18/24) of systemic reactions, and aeroallergen were reported to be responsible for 17% (4 of 24).

In a prospective study conducted over a 12-month period involving 1456 adult patients, the overall incidence of systemic reactions to skin tests, including SPTs and intradermal tests (IDTs), was 3.6% (52 patients), with an incidence of 0.4% (6 patients) for SPTs and 3.2% for IDTs. All patients who experienced systemic reactions with SPTs were reported to be sensitized to aeroallergen, but 5 of them were also sensitized to food allergens (11).

In a multi-center study conducted in 11 pediatric units, adverse reactions to 39.705 SPTs performed in 5908 children (with fresh food, aeroallergens and drugs) were evaluated. Seven vasovagal syncope and 7 generalized systemic allergic reactions were reported, with a risk rate of 0.12% for both conditions. All children with systemic allergic reactions were ≤12 years of age; low age (<1 yr) and active eczema were reported as risk factors (12).

Liccardi et al. reported an adult case of anaphylaxis after SPT with aeroallergen and retrospectively evaluated reactions to SPTs with aeroallergen over a 10-year period in 55.105 patients from 4 major allergy services in Italy, and found no other systemic or anaphylactic reaction (13). Ozdemir retrospectively evaluated reactions to SPTs over a 6-year period in 12.529 children with the symptoms suggesting allergic diseases, and reported an adverse reaction rate of 0.07% (9 cases: 8 vasovagal syncope, 1 vomiting) with no systemic reaction or anaphylaxis (14).

Valesco et al. reported that a 17-year-old patient with allergic rhinitis who underwent SPT had eye itching, eyelid swelling, and rhinorrhoea symptoms after 2 hours. Aeroallergen sensitization with *Dermatophagoides pteronyssinus and Dermatophagoides farinae, Euroglyphus maynei and Blomia tropicalis* was determined, and the patient was treated with rupatadine for his symptoms(15).

Anaphylaxis following skin prick testing with aeroallergen was reported from Türkiye. According to a report from Türkiye, a 9-year-old patient who had two wheezy attacks in the previous two months and had a brother with physician-diagnosed asthma developed urticaria, respiratory distress, and hypotension five minutes after the SPT and was treated with intramuscular adrenaline. The skin test was strongly positive for pseudopodia for house dust mites (16).

Although the SPT is considered a safe test method for diagnosing allergic diseases and the frequency of systemic reactions is low, precautions should be taken because of the risk of severe adverse reactions. Furthermore, these tests should only be performed in medical facilities with appropriate setups where well-trained medical personnel are available to diagnose and treat anaphylaxis.

**Informed Consent:** The parents provided informed consent for the publication of this case report.

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CASE REPORT

# A Rare Cause of Prolonged Fever and Cervical Lymphadenopathy: Kikuchi Fujimoto Disease

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## ABSTRACT

Kikuchi Fujimato Disease (KFD) is a rare and benign cause of cervical lymphadenopathy associated with fever. It is important to be aware of this disease as it is included in the differential diagnosis of diseases with high morbidity and mortality, such as lymphoma and tuberculosis. This study presents a child diagnosed with KFD to raise awareness of the disease. A 15-year-old female patient was admitted with neck swelling, weight loss, and fever for three weeks without response to antibiotic treatment. On examination, her temperature was 38oC, she had 3-4 fixed, painful, and hard cervical lymph nodes in cervical chains, the spleen was palpable at 1.5 cm, the liver at 1 cm, and other systems examination was normal. Laboratory tests revealed a neutrophil count of 770/L, lymphocyte of 800/L, C-reactive protein of 16.99 mg/L, and erythrocyte sedimentation rate (ESR) of 120 mm/h. Her fever and fatigue persisted during hospitalization, and no tests reveals infectious diseases. Peripheral blood smears, bone marrow aspiration microscopy, and flow cytometry did not reveal any findings in favor of malignancy, and excisional lymph node biopsy was performed for diagnosis. Histopathological examination was consistent with Kikuchi Fujimoto Disease. Antinuclear antibody (ANA) positivity (+++). The patient's fever and partial lymphadenopathy resolved after 14 days of hospitalization, and the ESR decreased to 40 mm/h at 4 months. Systemic lupus erythematous (SLE) and hemophagocytosis can complicated KFD, so the follow-up patient continues. It is difficult to distinguish KFD from serious diseases clinically and in the laboratory. Differential diagnosis through histopathological evaluation is associated with the awareness of the clinician and the experience of the pathologist. With an early diagnosis, unnecessary examinations and treatments can be prevented.

**Keywords:** Kikuchi, Fujimato, lymphadenopathy, children

## INTRODUCTION

Kikuchi Fujimoto disease (KFD), also known as "necrotizing histiocytic lymphadenitis," is a rare disease that was first described in 1972 (1,2). Its frequency is higher among Asians, young women, and whites. The pathogenesis of this disease is not fully understood, and it is generally believed to be due to an autoimmune response to viral infection. The mechanism of cellular destruction was suggested to be apoptosis by cytotoxic CD8-positive T lymphocytes (3,4). Human herpesviruses 6 and 8, Epstein-Barr virüs, parvovirus B19, human immunodeficiency virus (HIV), parainfluenza virus, *Yersinia enterocolitica*, and *Toxoplasma* are some of the associated agents. The most common clinical manifestations are cervical lymphadenopathy and fever (30-50%) in previously healthy young women. Even if it was first described in women, it also occurs in men with a 1/4:1:6 ratio (5). Other symptoms include rash, fatigue, arthritis, and hepatosplenomegaly. KFD is a self-limiting disease. However, some studies have reported that it is associated with systemic lupus erythematosus (SLE), Still's disease, and subsequently, lymphoma, acute leukemia, and hemophagocytosis develop. The diagnosis of KFD is difficult, and misdiagnosis is not uncommon. Patients can be diagnosed as having lymphoma when physicians and pathologists are unfamiliar with this entity. This misdiagnosis leads to extensive investigations and treatment with cytotoxic agents (6). The aim of this study was to increase awareness regarding the diseases among physicians.

## CASE

A previously healthy 15-year-old girl was admitted with neck swelling, fever, myalgia, and weight loss lasting approximately 3 weeks. There was no clinical response to the empiric antibiotic administered at the previous admission. On physical examination she had 3-4 fixed, tender, and firm lymph nodes

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that formed clusters in the left cervical chain, the spleen was 1.5 cm palpable, and the liver was 1 cm palpable. Laboratory tests showed a white blood cell count of 1,800/L (4,500-13,000/uL), with 770/L, neutrophils (1,800-8000/uL) and 800/L lymphocytes (1,200-5,200), hemoglobin of 9.7 g/dL (>12), and platelets of 279,000/L. Kidney and liver function tests and coagulation values were within normal ranges. C-reactive protein (CRP) was 16.99 mg/L (<5 mg/L), LDH was 355 U/L (0-248 U/L), and erythrocyte sedimentation rate (ESR) was 120 mm/hour (<20mm/hour). Neck ultrasound showed numerous lymph nodes in all segments of both the right and left cervical areas, initially reactive, with the largest being 17x8 mm in diameter. After blood and urine cultures, empirical antibiotic therapy was initiated.

During hospitalization despite treatment patient's fever, myalgia and lymphadenopathy were persisted. Further tests were performed; immunoglobulins were in the normal range of IgA, 3.28 g/L; IgM, 0.71 g/L; IgG, 14.58 g/L; viral markers did not show any active infection; anti-CMV IgM, 0.22 U/mL; anti-CMV IgG, 498; EBV EBNA IgM negative; EBV EBNA IgG positive; HBsAg, 0.544; anti-HBs, 36.8; anti-HCV negative; antiHAV IgG, 1.12; antiHAV IgM, 0.31; and anti-HIV, 0.189. Brucella agglutination, *Bartonella henselae* IgG, and *Franciella tularensis* IgG were negative, tuberculin skin test (TST) was anergic, IGRA was negative, RF 6.2 IU/mL, ANA (+++), Anti-dsDNA <10 IU/mL, complement 3 (C3) level 1.18 g/L, C4 0.21 g/L, TSH 1.43 mIU/L, and free T4 was 1.16 ng/dL. Peripheral smear examination did not reveal any atypical cells. Bone marrow aspiration showed normocellular bone marrow with normoactive erythroid and myeloid cells without atypical cells, and flow cytometry did not reveal any evidence of malignancy. Abdominal ultrasonography revealed a normal-sized liver and spleen and not lymphadenopathy. Contrast-enhanced neck magnetic resonance imaging (MRI) revealed reactive lymph nodes on both sides of the neck triangle. Diagnosis could not be obtained with all the tests. Excisional biopsy of the largest cervical lymph node was performed. No microorganisms were detected in the pyogenic and mycobacterium culture, and the polymerase chain reaction was negative for *mycobacterium tuberculosis*. On the other hand, histopathological examination revealed small mature lymphocytes, immunoblastic cells, and numerous histiocytes with vascular proliferation. The histiocytes surruounded wide necrotic areas in various places (Figure 1). Widespread CD68 immunostaining confirmed histiocytic proliferation.  was confirmed by (Figure 2). The findings were interpreted as consistent with "necrotizing histiocytic lymphadenitis". The patient was diagnosed with KFD based on histopathological findings and clinical manifestations and laboratory findings. On the 14th day of hospitalization, antibiotic treatment was discontinued because the fever subsided spontaneously regardless of antibiotic treatment. On the 3rd week, the laboratory findings showed a white blood cell count of 4,600 /uL, neutrophil 2,610/uL, lymphocyte 1,400/uL, hemoglobin 12.4 g/dl, and platelet 311,000/uL. On the 4th month of follow-up, the patient's hemogram and biochemical values returned to normal ranges, with an ESR of 40 mm/hour, and a few lymphadenopathies 1 cm in diameter were seen in the posterior cervical triangle on neck ultrasound. She is currently being followed by the pediatric infectious disease, pediatric hematology, and pediatric rheumatology departments.

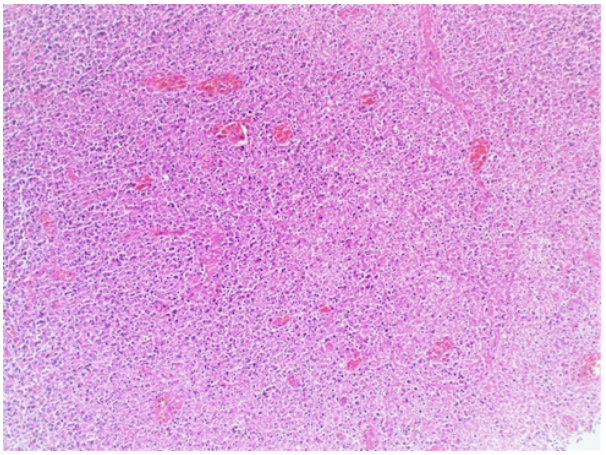

**Figure 1: (HEx100) necrotic areas and histiocytes.**

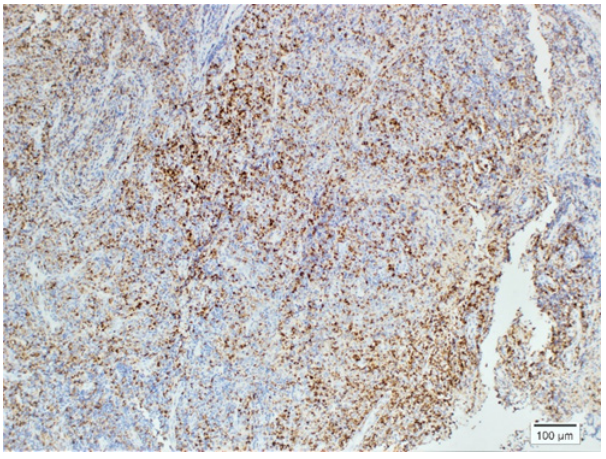


**Figure 2: (CD68x100) widespread histiocytic infiltration.**

Written informed consent was obtained from the patient and her parents for the presentation.

## DISCUSSION

KFD is often observed in women and individuals aged 40 years old (7,8). Regarding ethnic distribution, 75% of cases occur in white individuals, and it is most commonly observed in Asians. Accordingly, this case involved a 15-year-old female from Turkiye.

The strongest hypothesis regarding the pathogenesis of the disease is an inflammatory response by T cells and histiocytes to an infectious agent. Epstein-Barr virus (EBV), human herpes virus 6 (HHV6), human herpes virus 8 (HHV8), HIV, parvovirus B19, paramyxoviruses, and parainfluenza virus have been shown as triggering agents (9,10). Serological tests performed to find clues about the infectious agents that might be trigger for disease were nonspecific in this patient, and no etiologic triggering agent was shown.

In this case, the clinical manifestations were fever and myalgia accompanied by cervical lymphadenopathy, as observed in most patients with KFD. Lymphadenopathy is observed in all, fever in approximately 30-50% of patients and generally resolves in 7-10 days, sometimes it lasts about 3 weeks. The other expected clinical findings are rash (10%), fatigue (7%), arthritis, and hepatosplenomegaly (3%) (5). Lymph node involvement is usually characterized by unilateral involvement of the cervical lymph nodes and is painful. Bilateral cervical, axillary, mediastinal, and inguinal lymphadenopathy can also be observed. A typical lymphadenopathy picture is multiple, distinct lymph nodes with regular borders and a diameter of 1-2 cm. This case had 3-4 fixed, painful, and hard cervical lymph nodes in bilateral cervical chains. Although the patient had no extracervical lymph node involvement, involvement of abdominal, pelvic, and inguinal axillary lymph nodes has been reported in some cases of bilateral cervical disease and leukopenia.

There are no typical laboratory findings for the disease, and thus, differential diagnosis is challenging. In most patients, complete blood count parameters are normal, and leukopenia can be observed (43%), whereas thrombocytopenia and pancytopenia can also be seen in some cases (11,12). ESR is high in about 70% of cases. In this case, leukopenia, neutropenia, lymphopenia, and a high sedimentation rate were observed. The presence of fever, lymphadenopathy, cytopenia, and high sedimentation rate raised suspicion for malignancy; especially leukemia and lymphoma. In fact, the differential diagnosis of KFD includes infectious mononucleosis, tuberculosis lymphadenitis, systemic lupus erythematous, cat scratch disease, and malignancy. Ultrasonographic findings can also raise suspicion of lymphoma. Tuberculosis is another type of disease present in the differential diagnosis of KFD. However, compared with tuberculous lymphadenitis, lymph nodes in KFD are smaller, less round, have more echogenic hilus, appear less necrotic, and have less calcification (13). In the ultrasound images of this case, the lymph nodes appeared homogeneous and reactive. Histopathologic examination of lymph node biopsy is a diagnostic method and will show necrosis and histiocytic infiltration together in paracortical foci. In KFD, CD 8 (+) cytotoxic T cells are abundant around necrotic areas, which helps distinguish KFD from SLE and reactive lymph node hyperplasia. Furthermore, the absence of intact polymorphonuclear leukocytes in necrotic areas can help exclude infectious and malignancy-related conditions (such as HSV, Hodgkin's lymphoma). Histopathological findings on microscopic examination of the patient's lymph node material were consistent with necrotizing histiocytic lymphadenopathy, also known as KFD.

There is no proven treatment for KFD. Spontaneous recovery occurs within one to four months. Glucocorticoids or intravenous immunoglobulin therapies have been tried in cases with severe or prolonged manifestation, and significant benefits have been observed. Some patients have shown good response to hydroxychloroquine and interleukin-1 inhibitors (14-17). In our patient, the disease resolved spontaneously during observation. Recurrence of the disease is observed in approximately 10% of patients, and in 2.7% of patients, autoimmune disease has been reported to develop; therefore, monitoring for relapse or development of autoimmune disease, hemophagocytosis in the long term is logical. This case did not show any signs of autoimmune disease, but ANA became positive during follow-up, and she is currently being followed up by pediatric infectious disease, pediatric hematology, and oncology outpatient clinics.

## CONCLUSION

It is difficult to distinguish KFD from serious diseases clinically and in the laboratory. Differential diagnosis through histopathological evaluation is associated with the awareness of the clinician and the experience of the pathologist. With an early diagnosis, unnecessary examinations and treatments can be prevented.

**Informed Consent:** Written informed consent was obtained from the patient and her parents for the presentation.

**Peer Review:** Externally peer-reviewed.

**Author Contributions:** Conception/Design of Study- Ç.K., K.O.D., A.S., S.G., F.K., Z.Ü.A., C.Ö.; Data Acquisition- Ç.K., K.O.D., A.S., S.G., F.K., Z.Ü.A., C.Ö.; Data Analysis/Interpretation- Ç.K., K.O.D., A.S., S.G., F.K., Z.Ü.A., C.Ö.; Drafting Manuscript- Ç.K., K.O.D., A.S., S.G., F.K., Z.Ü.A., C.Ö.; Critical Revision of Manuscript- Ç.K., K.O.D., A.S., S.G., F.K., Z.Ü.A., C.Ö.; Final Approval and Accountability-Ç.K., K.O.D., A.S., S.G., F.K., Z.Ü.A., C.Ö.

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CASE REPORT

# Case Presentation: Large Diffuse B-cell Lymphoma Developing in the Context of Primary Immunodeficiency

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## ABSTRACT

Ataxia Telangiectasia (AT) is a rare, autosomal recessive neurodegenerative disorder characterized by immunodeficiency. Clinically, it is known to be associated with progressive cerebellar ataxia starting in early childhood, oculocutaneous telangiectasia, cellular and humoral immunodeficiency, and an associated increased risk of cancer. A 9-year-old female patient diagnosed with ataxia telangiectasia presented to the immunology outpatient clinic with complaints of difficulty breathing and snoring. Examination revealed an ulcerative vegetative mass obstructing the airway in the palate. The patient also presented with white plaques on her tongue, raising the possibility of fungal infection or lymphoproliferative disease. A biopsy of the palatal lesion was performed, and the patient was diagnosed with Diffuse Large B-Cell Lymphoma. Cultures from the biopsy also revealed simultaneous Candida albicans growth. This case highlights the increased risk of lymphoproliferative disorders in patients with primary immunodeficiency due to Ataxia Telangiectasia, which may present with a range of clinical manifestations. In this patient group, there is a potential association with invasive infections and malignancy, underscoring the need for clinicians to consider further investigations and, if necessary, perform a biopsy to support the diagnosis in cases of clinical suspicion.

**Keywords:** Ataxia Telangiectasia, Diffuse Large B-Cell Lymphoma, Fungal Infection

## INTRODUCTION

Cancer registry data (ICR) include information about the types of malignancies reported by patients with Ataxia Telangiectasia (AT). The largest category of malignancies in these patients comprised non-Hodgkin lymphomas and leukemias (64%), followed by other solid tumors (26%) and Hodgkin's disease (10%) (1). Recognizing the underlying immune deficiency in these patients is crucial because it may necessitate modifications to chemotherapy and radiation therapy protocols, making accurate diagnosis highly important.

Individuals with primary or secondary immunodeficiencies experience a significantly increased risk of infections and malignancies. Other syndromes associated with such increased risks include Wiskott-Aldrich Syndrome (WAS), common variable immunodeficiency (CVID), and severe combined immunodeficiency (SCID). Among these, patients with AT exhibited the highest incidence of malignancy, followed by CVID and WAS. According to cancer registry data, non-Hodgkin lymphoma is the most common malignancy among these disorders (2). Lymphomas in patients with AT form a highly heterogeneous group based on histological subtypes. Morphologically and in terms of cellular markers, these lymphomas more closely resemble those seen in children without immune deficiency than in patients with WAS and SCID.

The definitive diagnosis of AT is made by identifying homozygous or compound heterozygous mutations in the ATM gene. Supporting diagnostic findings include elevated serum AFP levels and reduced IgA and IgG levels. Cerebellar atrophy on MRI is another important diagnostic feature, whereas the presence of telangiectasias on physical examination is considered pathognomonic for AT.

In patients with congenital, acquired, or iatrogenic immunodeficiency, the risk of lymphoproliferative diseases is higher than that in the general population. Immunodeficiency-related lymphoproliferative diseases are categorized separately in the World Health Organization classification of hematopoietic and lymphoid system malignancies. These diseases exhibit clinical and pathological characteristics that differ from those of malignancies

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in the general population, depending on the underlying cause. Lymphomas, which are most commonly of B lymphocyte origin, typically display aggressive histopathological features and are frequently associated with Epstein–Barr virus (EBV). In immunodeficient patients, an insufficient cytotoxic T lymphocyte response to EBV leads to uncontrolled proliferation of EBV-infected B cells. In addition, inherited or acquired genetic alterations in oncogenes and tumor suppressor genes, chronic antigenic stimulation, and oncogenic viral infections can contribute to the development of lymphoproliferative diseases in immunodeficient individuals. Written consent was obtained from the parents.

## CASE PRESENTATION

Our patient is a 9-year-old girl, followed in the Pediatric Allergy and Immunology outpatient clinic with a diagnosis of Ataxia Telangiectasia (AT), which is a primary immunodeficiency and was receiving regular immunoglobulin support every 3 weeks. The patient is on prophylactic treatment with Trimethoprim-Sulfamethoxazole (TMP-SMX) for Pneumocystis jirovecii (PJP) and Fluconazole for fungal infection prophylaxis. Because of her primary immunodeficiency, she has a history of hospitalizations for pneumonia.

She presented to the Allergy and Immunology clinic with complaints of nasal congestion, difficulty breathing, and wheezing. On physical examination, a white plaque-covered mass was found on the soft palate, and a polypoid lesion was identified in the left nasal cavity (Figure 1). Given the differential diagnosis of malignancy and fungal infection, the patient was admitted for further evaluation. Laboratory results showed hemoglobin 12.3 g/dL, total leukocyte count 11,900 × 10^6/µL, absolute neutrophil count 9,200 × 10^6/µL, absolute lymphocyte count 600 × 10^6/µL, monocyte count 1,800 × 10^6/µL, lactate dehydrogenase (LDH) 288 U/L, uric acid 1.2 mg/dL, phosphorus 3.74 mg/dL, potassium 3.96 mg/dL, and creatine kinase 409 U/L. Epstein-Barr virus (EBV) DNA was negative, and immunoglobulin levels showed IgA at 4 mg/dL and IgG at 1,037 mg/dL. Given the defective DNA repair gene in AT, MRI was planned instead of a CT scan for imaging.

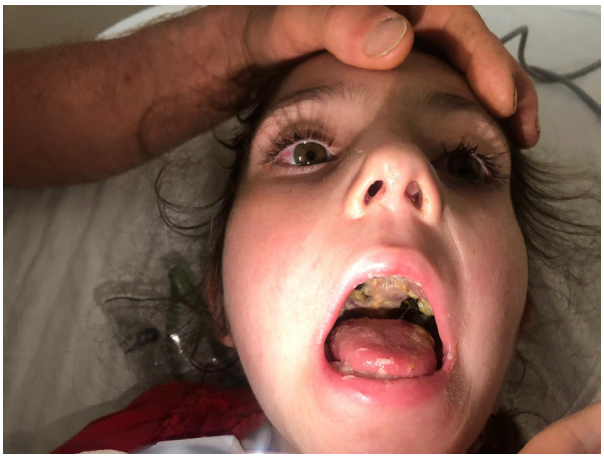

**Figure 1: Bilateral telangiectasias in the sclerae and a vegetative mass appearance on the palate.**

### Imaging Findings

Magnetic Resonance (MRI) imaging revealed a mass that obliterated the nasopharynx, with infiltration into the ethmoid, sphenoid, and frontal sinuses. The lesion was hypointense on T1- weighted imaging and heterogeneously isointense on T2-weighted imaging. After intravenous contrast administration, the lesion showed homogeneous enhancement and significant diffusion restriction, which are highly indicative of lymphoma. Additionally, a fistulous lesion was noted connecting the oral and nasal cavities (Figure 2).

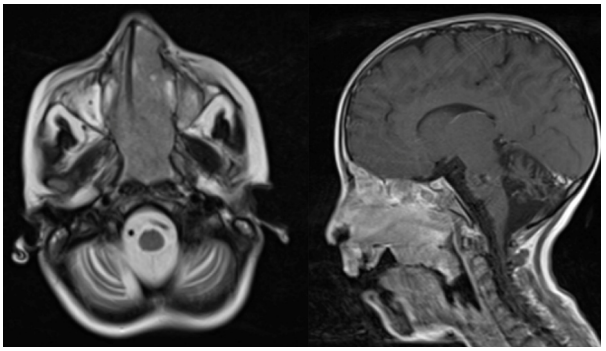

**Figure 2: Pre-treatment MRI image of the lesion.**

### Microbiological and Histopathological Findings

Culture of the lesion site revealed *Candida albicans*. Galactomannan antigen testing, which was performed to assess for possible invasive fungal infection, was negative. To evaluate for lymphoproliferative disorders, Tru-cut biopsy was performed on the lesion, and the diagnosis of Diffuse Large B-Cell Lymphoma (DLBCL) was confirmed.

Immunohistochemical analysis showed negative EBV staining.

### Further Investigations

Positron Emission Tomography-Computed Tomography (PET/CT) showed no hypermetabolic areas except for the nasal and oral cavities. Bone marrow aspiration and biopsy were performed, and no evidence of lymphoma involvement.

### Treatment

Given the diagnosis of stage II non-Hodgkin lymphoma (NHL) on the basis of primary immunodeficiency, the patient was started on the R-CHOP chemotherapy protocol, administered every 3 weeks. She was also started on antifungal treatment with Amphotericin B for the treatment of widespread *Candida albicans* infection and prophylaxis. After three cycles of chemotherapy, follow-up magnetic resonance imaging (MRI) revealed a complete response to treatment. After six cycles of R-CHOP chemotherapy, the patient completed her treatment protocol, and the decision was made to discontinue further therapy based on her risk group (Figure 3).

## DISCUSSION

Our patient, diagnosed with Ataxia Telangiectasia (AT) and chronic lung disease due to recurrent pulmonary infections,

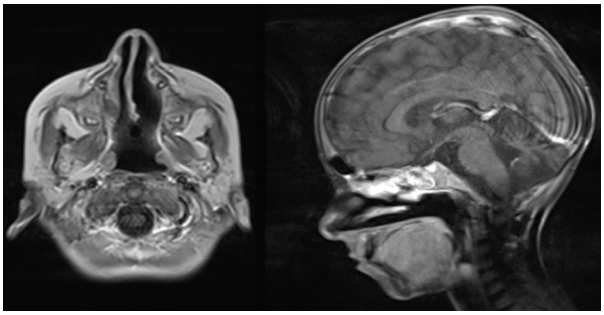

**Figure 3: Post-treatment magnetic resonance imaging image.**

tolerated the combination of rituximab and CHOP chemotherapy very well. Additionally, she did not experience long-term bone marrow suppression or severe febrile neutropenic episodes typically associated with chemotherapy, due to receiving regular intravenous immunoglobulin (IVIG) replacement therapy.

The combination of AT and lymphoma is extremely rare. In such cases, a personalized treatment approach is crucial. This underscores the importance of management by experienced teams with the potential for drug dose modifications when necessary. Consequently, our case highlights the need for an individualized approach for treating these complex patients (3). In patients with immunodeficiency, susceptibility to lymphoproliferative syndromes and EBV association should also be carefully considered. If serum EBV DNA levels are positive upon diagnosis, it is essential to monitor the trend of these levels during treatment (4).

In Ataxia Telangiectasia, defective cell cycle control leads to increased sensitivity to agents that cause DNA damage, such as radiation therapy and chemotherapy. This resulted in a higher propensity for malignancies, especially leukemia and lymphoma. Chronic lymphoproliferation due to antigenic stimulation following B and T cell activation, along with impaired apoptosis, contributes to the initiation of lymphoid proliferation (5).

The prognosis of lymphomas developing in the context of primary immunodeficiency is generally worse than that of immunocompetent individuals. In such cases, chemotherapy doses may need to be reduced to protect the patient from drug toxicity. However, this reduction can be concerning for clinicians because it may increase the risk of disease progression and relapse. Nonetheless, the primary goal remains to protect highly sensitive patients from the toxic effects of chemotherapy, thereby preventing complications related to increased infection frequency.

*Although rare, Candida albicans* can cause invasive fungal infections in immunocompromised individuals (6). It is important to remember that the natural course of infections may differ between immunodeficient and immunocompetent patients (7). In our case, chemotherapy was well managed and infection control was successfully achieved, providing a rare example of lymphoma development in the context of primary immunodeficiency. This case may serve as a valuable reference for clinicians managing similar cases of immunodeficiency–associated malignancy.

This case highlights the need for careful monitoring and management in immunocompromised patients, emphasizing individualized treatment plans that consider both the primary immunodeficiency and the risks of malignancy and infection.

**Informed Consent:** Written consent was obtained from the participants.

**Peer Review:** Externally peer-reviewed.

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

**Conflict of Interest:** Authors declared no conflict of interest.

**Financial Disclosure:** Authors declared no financial support.

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LETTER TO THE EDITOR

# Can SARS-CoV-2 Be a Potential Cause of Microcephaly?

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Dear Editor,

Microcephaly (MC) is defined as a head circumference with a standard deviation score (SDS) below -2 according to some experts and below -3 according to others (1-3). In our clinic, we use the criterion of head circumference below -2 SDS to define MC. MC can be classified as primary if present at birth, or as secondary if it develops postnatally (2, 4, 5). Several risk factors have been associated with MC, including genetic disorders, teratogenic exposure, maternal age, maternal phenylketonuria, and hypoxic-ischemic encephalopathy. Keskindemirci et al. also highlighted that socioeconomic factors may play a role in the risk of MC (6). Among these, maternal infections during pregnancy are the leading causes of microcephaly, with Rubella, Zika virus, and cytomegalovirus (CMV) being the most recognized infectious etiologies (2, 4).

The impact of COVID-19 on fetal development during pregnancy has not been fully elucidated. There are reports in the literature suggesting that SARS-CoV-2 infection during pregnancy may lead to complications (7). We read with interest the recent article by Edlow et al., which concluded that "COVID-19 exposure may be associated with neurodevelopmental changes and highlights the need for prospective investigation of outcomes in children exposed to COVID-19 in utero" (8). Moreover, Auger et al., in their time series analysis, observed an increased frequency of microcephaly during the COVID-19 pandemic period (9).

Considering these findings, we wish to share our own observations, which are consistent with those reported by Edlow et al. and Auger et al. Our well-child unit has noted a relative increase in the number of primary microcephaly cases during the COVID-19 pandemic. From January 2002 to March 2020, we identified 49 children with microcephaly, 30 of whom were diagnosed with primary microcephaly. Between 2006 and 2021, the median incidence of primary microcephaly was 2 cases per year, and the range was 0-4. However, in 2021, 8 new cases of primary microcephaly were documented—all of which involved infants born in that year. Further investigation revealed that all the mothers were pregnant and gave birth during the pandemic period (March 2020 to March 2022). Among these mothers, three were confirmed to have had COVID-19 during the second trimester via laboratory tests, while two others reported upper respiratory infections during the same period, although laboratory tests were not conducted.

In conclusion, our observations suggest that maternal COVID-19 infection during pregnancy may contribute to the increased incidence of microcephaly during the pandemic. To better

**Supplementary Table: The distribution of primary microcephaly diagnoses by year**

| Years of Birth | n |
|---|---|
| 2006 | 1 |
| 2007 | 1 |
| 2008 | 1 |
| 2009 | 3 |
| 2010 | 3 |
| 2011 | 3 |
| 2012 | 1 |
| 2013 | 4 |
| 2014 | 1 |
| 2015 | 2 |
| 2016 | 3 |
| 2017 | 1 |
| 2018 | 3 |
| 2019 | 3 |
| 2020 | 0 |
| 2021 | 8 |
| 2022 | 0 |
| Total | 38 |

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understand the potential association between COVID-19 and microcephaly, we recommend conducting multicenter studies involving larger cohorts. The supplementary table presents the distribution of primary microcephaly diagnoses by years.

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