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ORIGINAL ARTICLES

CASE REPORT

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Original Article

The Role of *ATRX* and *TERT* Expressions in Determining Aggressiveness of Neuroblastoma

ATRX ve TERT Ekspresyonunun Nöroblastom Agresifliğini Belirlemedeki Rolü

Murat Tuncel[1], Selen Kum Özşengezer[1], Gamze Sanlav[1], Deniz Kızmazoğlu[2], Safiye Aktaş[1], Zekiye Altun[1], Tekincan Çağrı Aktaş[1], Erdener Özer[3], Nur Olgun[2]

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ABSTRACT

Objective: Neuroblastoma (NB) is a common childhood tumour, affecting telomerase enzyme activity. Expression of telomerase reverse transcriptase (*TERT*) protein is crucial for the fuınctioning of telomerase activity, but its association with risk stratification and prognosis is unclear. The adenosine triphosphate-dependent helicase alpha-thalassemia/mental retardation x-linked (*ATRX*) protein, a chromatin remodeling protein, accumulates H3.3 histone variants. The study aimed to assess the correlation between expression levels of *ATRX* and *TERT* with the NB risk group and its prognosis.

Method: Immunohistochemical expressions of *TERT* and *ATRX* proteins in tumour tissue samples of 54 NB cases at different stages and risk groups were evaluated.

Results: Immunohistochemical expression rates of *TERT* and *ATRX* proteins in tissues were 55.8% and 61.2%, respectively, with ATRX positively expressed at a rate of 50%, and 69% in early and in advanced stages of NB, and rates of 67.7%, and 50% in high and low-risk groups, respectively. *TERT* expression varies in early and advanced stages of NB, with higher levels in high-risk groups. *ATRX* expression is significantly higher in NB patients with *Neuroblastoma myc (NMYC)* gene amplification.

Conclusion: High expression of *ATRX* in NB patients with *NMYC* gene amplification suggests that *ATRX* may be used as a potential immunohistochemical prognostic marker in NB patients.

Keywords: Neuroblastoma, *TERT*, *ATRX*, immunohistochemistry

ÖZ

Amaç: Nöroblastom (NB), telomeraz enzim aktivitesini etkileyen yaygın bir çocukluk çağı tümörüdür. *TERT* ekspresyonu telomeraz aktivitesi için çok önemlidir, ancak risk sınıflandırması ve prognoz ile ilişkisi belirsizdir. Bir kromatin yeniden şekillendirme proteini olan adenozin trifosfat bağımlı helikaz alfa-talesemi/zeka geriliği, X'e bağlı (*ATRX*), H3.3 histon varyantlarını biriktirir. Bu çalışmada *ATRX* ve *TERT* ekspresyon düzeyleri ile NB risk grubu ve prognoz arasındaki ilişkinin değerlendirilmesi amaçlanmıştır.

Yöntem: Farklı evre ve risk gruplarındaki 54 NB olgusunun tümör dokusu örneklerinde immünohistokimyasal telomeraz ters transkriptaz (*TERT*) ve *ATRX* protein ekspresyonları değerlendirildi.

Bulgular: Dokularda *TERT* ve *ATRX* ekspresyonu sırasıyla %55,8 ve %61,2 idi ve *ATRX* erken evrelerde %50 ve yüksek evrelerde %69 oranında pozitif eksprese edildi. Yüksek riskli gruplarda %67,7 ve düşük riskli gruplarda %50 ekspresyon göstermiştir. *TERT* ekspresyonu erken ve yüksek evrelerde değişkenlik gösterirken, yüksek riskli gruplarda daha yüksek seviyelerdedir. *ATRX* ekspresyonu *NMYC* amplifikasyonu olan NB hastalarında anlamlı derecede yüksektir.

Sonuç: *NMYC* amplifikasyonu olan NB hastalarında *ATRX*'in yüksek ekspresyonu, *ATRX*'in NB hastalarında potansiyel bir immünohistokimyasal prognostik belirteç olarak kullanılabileceğini düşündürmektedir.

Anahtar kelimeler: Nöroblastom, *TERT*, *ATRX*, immünohistokimya

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INTRODUCTION

Neuroblastoma (NB) is the most common extracranial solid tumour in children. This tumour, which is frequently seen in children younger than two years of age, is defined in 90% of children younger than five years of age[1]. NB may show spontaneous regression or benign transformation to ganglinouroma especially in patients under 1 year of age. In patients over 1 year of age, the disease has a more aggressive course[1]. Genetic changes play an important role in the prognosis and treatment of the disease[2]. In the risk classification made for the treatment of the disease, genetic mutations and chromosomal changes in the patient are also examined in addition to the patient's age, tumour stage and histology[3,4]. MYCN oncogene amplification is an amplification observed in 20-30% of NB patients and is associated with poor prognosis[5] In advanced NB patients with *MYCN* amplification, event-free and overall survival (OS) rates are reported to be considerably lower compared to the patients without[6]. According to the The Turkish Pediatric Oncology Group (TPOG) - NB 2009 Protocol study conducted between 2009 and 2020, 70% of the patients diagnosed in Türkiye had advanced disease and 59% of these patients were in the high risk group according to the NB diagnosis and treatment protocol[4]. The tumour suppressor gene alpha-thalassemia/mental retardation X-linked (*ATRX*) blocks DNA replication and transcription by taking part in a chromatin remodelling whose main function is the accumulation of histone variant H3.3[7]. *ATRX* mutations are commonly found in glioma and are associated with the development of alternative telomere lengthening (ALT), a non-telomerase-dependent telomere lengthening mechanism[8]. In addition to its known roles, it influences various cellular processes associated with epigenetic regulation[9]. The loss of *ATRX* can arise through gene mutations, deletions, or chromosomal rearrangements such as gene fusions. The ALT phenotype is frequently linked to distinct molecular changes, including amplification of the platelet-derived growth factor receptor-alpha and mutations in the tumour suppressor gene tumor tumor protein p53. In most NB cells, upregulation of telomerase activity or activation of the ALT pathway results in activation of telomere maintenance mechanisms. Activation of the ALT pathway is mostly caused by mutations in the *ATRX* gene. As a result of this activation, telomeres elongate leading to carcinogenesis. *ATRX* mutations are observed especially in NB patients older than 18 months and show a positive correlation with age[7]. Telomerase is a key enzyme involved in regulating cell proliferation and tumorigenesis. It maintains chromosomal integrity by adding hexameric sequences to the ends of chromosomes, thereby preventing telomere shortening and the onset of cellular senescence. The catalytic subunit of human telomerase, known as *hTERT*, serves as the primary rate-limiting component for telomerase activity[10]. This enzyme is active in over 90% of human malignancies. In cancer, telomerase reverse transcriptase (*TERT*) expression can be elevated through multiple mechanisms, such as gene amplifications, promoter mutations, and chromosomal rearrangements. Notably, promoter rearrangements of *TERT* have been identified in high-risk NB cases[11]. In NB, determination of prognostic markers that can provide information about the risk groups and prognosis of patients is very important both for the development of targeted therapies and for obtaining better treatment results. Some molecules that may play a role in the prognosis of NB or treatment response continue to be revealed[12-17]. In this study, we investigated *TERT* and *ATRX* protein expressions in tumour tissues of early-and late- stage NB patients from different NB risk groups and evaluated whether or not their expression levels could be differentiating markers in terms of aggressiveness in early- and late- stages of NB by revealing their relationship with NB risk groups and prognosis.

MATERIALS and METHODS

Experimental Groups

Permission was obtained from Dokuz Eylül University (DEU) Non-Interventional Research Ethics Committee for the conduction of this research study (decision no: 2023/14-10, dated: 03.05.2023). Signed consent forms were obtained from the patients during the sample collection and storage stages. The study was carried out using tumour paraffin tissue samples of 53 NB patients submitted to DEU Institute of Oncology Department of Basic Oncology within the scope of TPOG-2020 protocol. Tissue samples of NB patients whose molecular analyses were performed and known to be in low and advanced stages of NB were used in the study[12,18].

Study population of 53 people consisted of 22 girls and 31 boys (Table 1). In NB, stage L1 refers to localised tumours confined within a single anatomical compartment without any image-defined risk factors (IDRFs). Stage L2 is characterised by regional tumours with the presence of IDRFs. The tumour may extend into different compartments on the ipsilateral side of the body. Stage M includes cases with distant metastatic spread. Involvement of the bone, liver, distant lymph nodes, or

Table 1. Characteristic features of patients with neuroblastoma

Characteristic	Total (n=53)
Age (months) (mean ± SD)	22.95±27.21
Gender, n (%)	
Female	22 (41.5)
Male	31 (58.5)
Risk groups, n (%)	
Low	18 (34.0)
Intermediate	9 (17.0)
High	22 (41.5)
***MYCN* AMP, n (%)**	
Positive	15 (28.3)
Negative	37 (69.8)
EFS (months) (mean ± SD)	21.39±27.01 (n=44)
OS (months) (mean ±SD)	24.70±26.62 (n=44)

Note: The International Neuroblastoma Risk Group Staging System (INRGSS) classification is used to determine the risk groups, and characteristic features of 53 study participants were stratified based on the criteria established by the Turkish Pediatric Oncology Group-2020 and INSS.
AMP: Amplification, EFS: Event-free survival, OS: Overall survival

pleural/abdominal effusion containing malignant cells outside the primary site indicates metastatic disease. Finally, stage MS represents a special form of metastatic disease that occurs only in patients younger than 18 months. It is defined by limited involvement of the skin, liver, and/or bone marrow (less than 10% of total marrow cellularity)[1]. In NB molecular analyses, real-time polymerase chain reaction (RT-PCR) analyses were performed to detect *NMYC*, 11q, 1p and 17q. Out of 53 patients, 22 were in the high-risk, 9 in the intermediate-risk and 18 in the low-risk group.

MYCN amplification status was defined based on RT-PCR results, with samples showing greater than a 10-fold increase were classified as positive, and those below this threshold as negative. As part of the TPOG study, NB Formalin-Fixed Paraffin-Embedded tissue samples at various disease stages were randomly selected from the archival collection of the Departments of Paediatric Oncology and Basic Oncology at Dokuz Eylül University. Tumour sections were cut from paraffin-embedded blocks and mounted on adhesive slides for immunohistochemical (IHC) analysis of ATRX and *TERT* protein expressions. According to the TPOG-2020 classification system, the patients were categorised into high-risk (n=22), intermediate-risk (n=9), and low-risk (n=18) groups[4,19].

Antibodies

In this study polyclonal human *ATRX* and *TERT* antibodies (Bioss, Inc. 500 West Cummings ParkSuite 6500 Woburn, MA, USA) were used, along with a secondary antibody obtained from Ventana. All antibodies were stored in accordance with the manufacturers' recommendations, and appropriate dilution ratios were observed during application. Optimal dilutions were determined through control staining, with both *ATRX* and *TERT* antibodies used at a 1:100 dilution. Paraffin-embedded tissue blocks of tumour specimens of NB patients were selected to represent all three risk categories to ensure comprehensive analysis across the disease spectrum.

IHC Staining

Tissue sections were incubated overnight at 60 °C in an oven prior to application of the staining procedure[18]. Following incubation, the slides underwent deparaffinization in xylene for one hour, and were subsequently rehydrated using a graded series of alcohol solutions. Antigen retrieval was achieved by heating the slides in citrate buffer using a microwave. After treatment with hydrogen peroxide and appropriate washing steps, human-specific primary Immunoglobulin G antibodies were applied, based on prior optimization. Subsequently, a multimer Horseradish Peroxidase-conjugated secondary antibody was added and allowed to incubate. In the final staining step, diaminobenzidine combined with hydrogen peroxide was used to catalyze the chromogenic reaction. The nuclei of the tumour cells were then counterstained with haematoxylin, and the slides were passed through an ascending alcohol series before being cleared in xylene. The prepared slides were examined under a light microscope (Olympus BX50). *ATRX* expression was detected in the nuclei, whereas *TERT* protein exhibited both nuclear and cytoplasmic localization. To evaluate staining intensities of *ATRX* and *TERT*, five randomly selected fields per section were analyzed for each sample. Tumour cell staining intensities were classified as follows: 0= no staining; 1= weak; 2= moderate; 3= strong. Additionally, the proportion of stained cells for *ATRX* and *TERT* was scored as 0= none; 1=0-20%; 2=21-50%; 3=51-80%; 4=81-100%. Given the strong correlation between staining intensities and area scores, the intensity score was utilized for statistical analysis in this study[20,21].

Determination of *NMYC* and 11q by RT-PCR and Flow Cytometry in Molecular Evaluation

Paraffin-embedded NB tissue samples were used for DNA isolation, and concentrations were quantified fluorimetrically using a Qubit® fluorometer. RT-PCR was performed to assess *N-MYCN* amplification and 11q23 deletion. Threshold cycle values were determined for target and reference genes in patient and control DNA samples. Copy number alterations were detected using specific primers and TaqMan probes:

for *N-MYCN*, primers 5′-GTGCTCTTCCAATTCTCGCCT-3′ and 5′-GATGGCCTAGAGGAGGGCT-3′ with a 6-carboxyfluorescein(FAM)-labeledTaqManprobe;for11q23 (*ARCN1* gene), primers 5′-ATCTGGAGGCAGCACAGCT-3′ and 5′ TACACTGGATTATACCCTGGCTGG-3′ with a FAM-labeled probe. PCR reactions were performed in eight replicates on a Roche Nano RT-PCR system. Relative quantification was calculated using the ΔΔCT method with healthy reference DNA as a calibrator, and findings were further validated via absolute quantitation using reference DNA standards (Table 2)[12,18].

Multivariate Survival Analysis

The patients included in the study were clinically categorised according to disease stage and risk classification. Patients were also categorised according to the molecular, and histological characteristics of the tumour, and age at diagnosis. The risk assessment and disease stage of the patients were considered to be confounding variables. Therefore, multivariate Cox regression survival analysis including the previously mentioned confounding factors was performed to confirm our findings. Cox regression analysis using different models showed that *ATRX* and *TERT* did not differ in univariate survival analysis. Again, no statistically significant difference was found between these parameters in multivariate Cox regression analysis. However, in the models created in Cox regression analysis, a significant relationship was detected between N-MYC Amp in NB patients and event-free survival (EFS) and OS rates (Table 3).

Statistical Analysis

We used Fisher's exact test to assess the relationship between categorical variables and *ATRX* and *TERT* expression patterns. The Independent Samples t-test was used to compare mean EFS and OS times between groups. Data were presented as mean ± standard deviation and the number of observations. EFS was defined as the time to the emergence of recurrence, secondary malignancy, or death. OS analysis included the interval from study registration to death or last follow-up. Survival curves were generated using the Kaplan-Meier method, and differences were tested using the log-rank test. All statistical analyses were conducted using IBM SPSS Statistics Version 29 (IBM Corp., USA), with p-values <0.05 considered statistically significant.

RESULTS

Data on the Clinicopathology of NB Patients

In this study, tissue samples from 22 female, and 31 male patients diagnosed with NB were analysed. The patients' ages ranged from 1 month to 11 years. Staging was performed in accordance with the criteria established by the Turkish Paediatric Oncology Group (2020) and the International Neuroblastoma Staging System. Risk stratification was based on the International Neuroblastoma Risk Group Staging System (INRGSS). According to the applied classification system, patients were categorised in the high (n=22), intermediate (n=9), and low-risk (n=18) groups, respectively (Table 1).

Risk Cassifications of Patients

Twenty-two-high, nine intermediate, and eighteen low-risk patients were analysed in this study. Both molecular (*MYCN* amplification, 11q23 loss and DNA index) and clinical (age of the patient, stage and histopathology of the tumour) data of patients were evaluated for the risk classification (Table 4).

Association of Age with Molecular Alterations and Survival Outcomes

To assess the prognostic impact of age, patients were stratified into two groups based on the well-established prognostic cut-off of 5 years of age (<5 years, n=38; ≥5 years, n=15). Loss of ATRX nuclear expression (negative staining) was significantly more frequently detected in patients aged 5 years or older compared to younger patients (46.7% vs. 15.8%, p=0.021). Similarly, a non-significant trend towards higher *TERT* expression was observed in the older age group (73.3% vs. 50%, p=0.13). Kaplan-Meier survival analysis revealed that patients ≥5 years of age had significantly worse OS compared to those <5 years (5-year OS: 40% vs. 78%, p=0.009 by log-rank test). EFS also followed a similar though non-significant, trend (5-year EFS: 33% vs. 63%, p=0.058). In a multivariate Cox regression model adjusted for *MYCN* amplification status and INRGSS risk groups, age ≥5 years remained an independent predictor of poorer OS [hazard ratio (HR): 3.2, 95%, confidence interval (CI): 1.1-9.3, p=0.032].

Expression of *TERT* and *ATRX* in Tissue Samples of Patients

In tissue samples, *TERT* and *ATRX* were expressed in 55.8% and 61.2% of cases, respectively. In NB, *ATRX* expression increased with disease stage, and observed in 50% of early-stage and 69% of advanced-stage tumours.

Similarly, *ATRX* expression was higher in high-risk patients (67.7%) compared to low-risk patients (50%). *TERT* was expressed at a rate of 55% in the early stage and 62.1% in the advanced stage. *TERT* was expressed at a rate of 58.1% in high-risk groups and 55.6% in low-risk groups. *ATRX* and *TERT* alterations were common in *MYCN*-amplified tumours (*ATRX* 86.7%, 13/15; 95% CI: 62.1-96.3; *TERT* 73.3%, 11/15; 95% CI: 48.0-89.1). In *MYCN*-non-amplified cases, the corresponding frequencies were 61.2% (23/38; 95% CI: 44.7-74.4) and 55.8% (21/38; 95% CI: 39.7-69.9), respectively. No significant differences were observed between groups in terms of expression rates of these risk predictors (*ATRX*: p=0.10; *TERT*: p=0.35). *ATRX* expression was found to be significantly higher in NB patients with *MYCN* amplification compared to patients without (p=0.027) (Figure 1 and 2).

Association Between ATRX and *TERT* Expressions and EFS and OS in High and Low Risk Groups in NB

The prognostic value of *ATRX* and *TERT* expressions in NB was assessed by stratifying patients into "high" and "low" expression groups. Associations between gene expression and OS, EFS, event occurrence, and risk classification were evaluated using Kaplan-Meier analysis,

Table 2. RT-PCR results for *MYCN* amplification and 11q values

Patient	*MYCN* Amp	11q	Patient	*MYCN* Amp	11q
No: 1	933.254	6879228.0000	No: 16	13.798	1.1745
No: 2	34.134	0.3140	No: 17	7.458	0.3290
No: 3	0.926	0.6250	No: 18	5.827	0.0040
No: 4	216.665	0.0002	No: 19	0.297	0.1540
No: 5	0.742	1.9250	No: 20	6.207	0.3890
No: 6	0.055	0.0630	No: 21	7.299	0.1740
No: 7	10.849	1.6280	No: 22	61.206	0.9450
No: 8	5.003	17.0170	No: 23	3.079	3.8390
No: 9	0.948	1.8970	No: 24	0.011	7.9510
No: 10	0.545	1.5900	No: 25	1.376	0.8820
No: 11	2.071	4.6410	No: 26	1.713	0.2800
No: 12	107.733	3.5030	No: 27	1.190	0.0380
No: 13	2.825	5.4140	No: 28	0.774	10.7502
No: 14	2.025	0.5110	No: 29	2.134	0.0700
No: 15	32.314	1.1850	No: 30	59.923	11.5720
No: 31	0.856	0.3240	No: 46	25.654	5.7430
No: 32	4.535	0.1540	No: 47	0.578	0.3800
No: 33	47.583	0.2440	No: 48	3.598	1.2000
No: 34	3.200	11.5950	No: 49	0.683	0.2450
No: 35	2.376	0.3370	No: 50	12.792	0.7170
No: 36	4.322	1.1850	No:51	10.792	1.1060
No: 37	0.981	0.4210	No: 52	0.591	0.0900
No: 38	0.385	0.8780	No: 53	3.338	1.2340
No: 39	23.065	0.5170			
No: 40	54.221	0.4190			
No: 41	0.922	0.4350			
No: 42	5.688	0.0080			
No: 43	2.604	0.2630			
No: 44	1.023	22702.5490			
No: 45	1.508	0.3226			

2p24.3 (*MYCN*) amplification and 11q23 (*ARCN1*) deletion of DNA samples were evaluated by TaqMan real-time PCR (RT-PCR) (Roche LightCycler Nano) with TaqMan labelled primers specifically designed for each relevant gene region. *N-MYC* amplicons and 11q aberrations of the patients are given in Table 3.
RT-PCR: Real-time PCR: Polymerase chain reaction

Table 3. Modeling of the results of Cox regression analysis								
Model 1								
	B	**SE**	**Wald**	**df**	**Sig.**	**Exp(B)**	**95.0% CI for Exp(B)**	
							Lower	**Upper**
TERT	-0.695	0.850	0.669	1	0.414	0.499	0.094	2.642
ATRX2	0.865	0.770	1.261	1	0.261	2.374	0.525	10.741
N-MYC Amp	1.930	0.817	5.584	1	0.018	6.893	1.390	34.177
Model 2								
	B	**SE**	**Wald**	**df**	**Sig.**	**Exp(B)**	**95.0% CI for Exp(B)**	
							Lower	**Upper**
TERT	-1.045	0.917	1.299	1	0.254	0.352	0.058	2.122
ATRX2	0.655	0.798	0.674	1	0.412	1.925	0.403	9.194
N-MYC Amp	2.055	0.885	5.390	1	0.020	7.803	1.377	44.213
Risk 2 factor	-0.129	1.138	0.013	1	0.910	0.879	0.095	8.170

Model 1 comprises three independent variables. Model 2 was employed to generate a new model with four independent variables by incorporating an additional independent variable. The values obtained are statistically significant at p<0.05.
B: Beta coefficient, SE: Standard error, CI: Confidence interval

Table 4. Summary of molecular characteristics and risk stratifications				
a) Distribution of risk groups by *MYCN* amplification and 11q status				
	High risk (n=22) n (%)	**Intermediate risk (n=9) n (%)**	**Low risk (n=18) n (%)**	**Total (n=49)**
***MYCN* amplified (n=15)**	13 (86.7)	0 (0)	2 (13.3%)	15
***MYCN* non-amplified (n=38)**	9 (23.7)	9 (23.7)	16 (42.1)	34*
11q deletion (n=25)	13 (52.0)	6 (24.0)	6 (24.0)	25
No 11q deletion (n=28)	9 (32.1)	3 (10.7)	12 (42.9)	24**

*As the risk groups of 4 out of 53 patients were not specified, relevant data of the remaining 49 patients are presented
**Data of 24 out of 34 patients.

b) Correlations between *MYCN* amplification and 11q deletion			
	11q deletion (+)	**11q deletion (-)**	**Total**
***MYCN* (+)**	4	11	15
***MYCN* (-)**	21	17	38
Total	25	28	53

*Fisher's exact test p-value=0.145
Molecular analysis revealed the distribution of risk groups, *MYCN* amplification, and 11q23 deletion.

with group comparisons conducted via the log-rank test. No significant differences were observed in terms of OS or EFS between *ATRX*-defined groups (OS: p=0.294; EFS: p=0.337) and *TERT*-defined groups (OS: p=0.693; EFS: p=0.740). Additionally, expressions of *ATRX* and *TERT* showed no significant correlation with event occurrence or risk classification (all p>0.05). Kaplan-Meier curves indicated substantial overlap in survival probabilities across expression-defined groups.

These results suggest that expressions of *ATRX* and *TERT* per se are not independent prognostic indicators in this cohort and are insufficient to predict survival outcomes. Their potential clinical utility may require their integration with additional molecular markers in a multivariate analytical framework. The corresponding survival curves are shown in Figure 3.

DISCUSSION

Ongoing advancements in NB research have contributed to a modest improvement in patient prognosis over recent years, with a corresponding increase in the 5-year survival rates. While patients with low-risk NB have shown relatively high cure rates, outcomes for patients with high-risk NB have remained largely unchanged. As such, elucidating the molecular characteristics and genetic alterations underlying NB is critical for developing strategies that enable early diagnosis and implementation of targeted therapeutic approaches[22]. Notably, *ATRX* mutations and the loss of nuclear protein expression have been observed more commonly in patients over the age of 12 who present with stage 4 disease. In a study by Cheung et al.[23], *ATRX* gene deletions were identified in 43% of older adolescents with advanced NB (>12 years) and in 11% of paediatric patients aged 5-12 years. Similarly, in our study, OS rates were significantly worse in the ≥5 age group, and age was found to be an independent risk factor in multivariate analysis, independent of other prognostic parameters such as *MYCN* status and risk group. These findings suggest that age is associated not only with clinical stage and molecular alterations, but also with tumour biology, including loss of *ATRX* mutations and telomere mechanisms. Therefore, age is a strong prognostic marker in NB that reflects molecular subgroups beyond classical risk classifications.

According to Clusters of Orthologous Genes database data, survival was significantly preserved in patients assigned to less intensive treatment due to the change in the age threshold from 12 to 18 months. This finding supports that biologically "more favourable" tumours in younger age groups do not always require intensive treatment and that age can be safely used as a variable in intensification of treatment. In this study, the better prognosis of the <5 age group also demonstrates that the younger age group has biologically more "favourable" tumours and can achieve better survival without requiring intensive treatment[24].

Data from a separate study related to the ≥5 year- and adolescent/young adult categories have shown a progressive, and significant drop in survival rates with advancing age. adolescent/young and adult patients

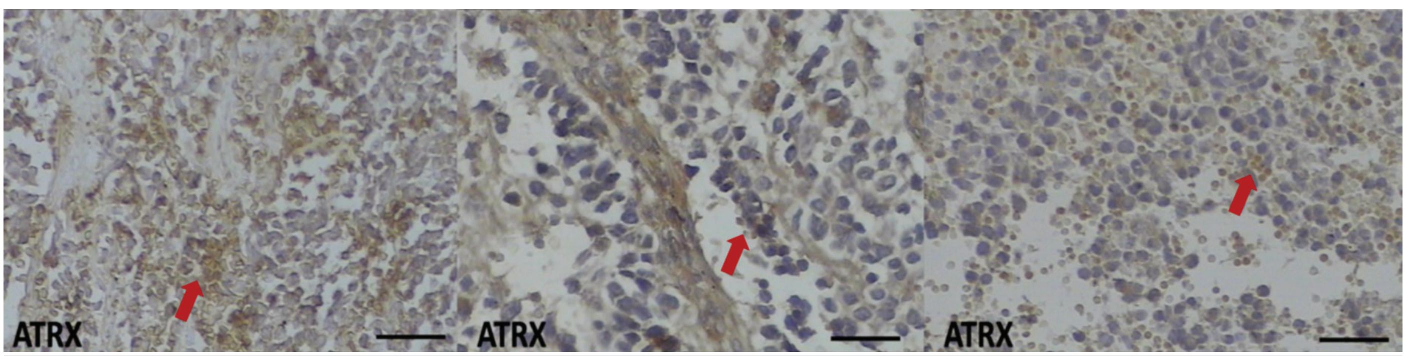

Figure 1. Immunohistochemical staining for ATRX in a neuroblatoma patient

This tissue sample obtained from neuroblastoma patient demonstrates a high rate of positive nuclear staining for ATRX as shown with red arrows (20X). ATRX was diluted 1:100.

ATRX: Alpha-thalassemia/mental retardation x-linked

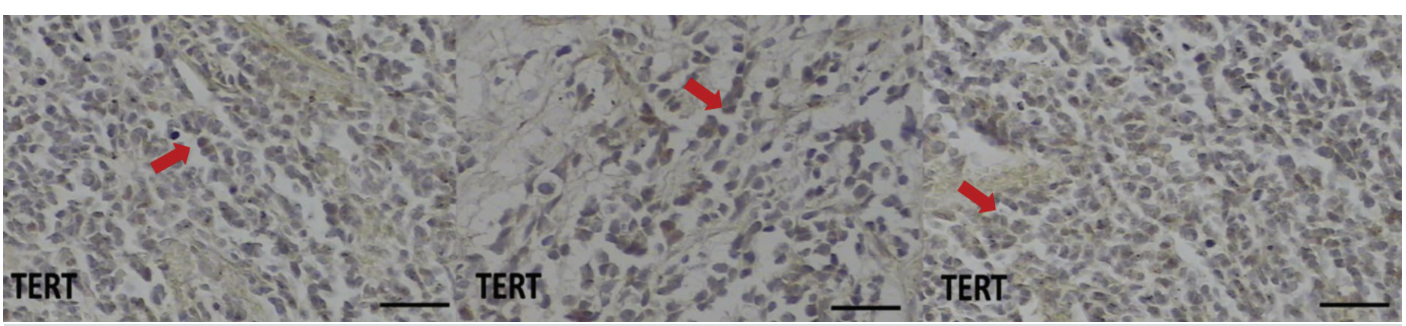

Figure 2. Immunohistochemical staining for TERT in a neuroblatoma patient

This tissue sample obtained from neuroblastoma patient demonstrates both positive nuclear and cytoplasmic staining for TERT as shown with red arrows (20X). TERT was diluted 1:100.

TERT: Telomerase reverse transcriptase

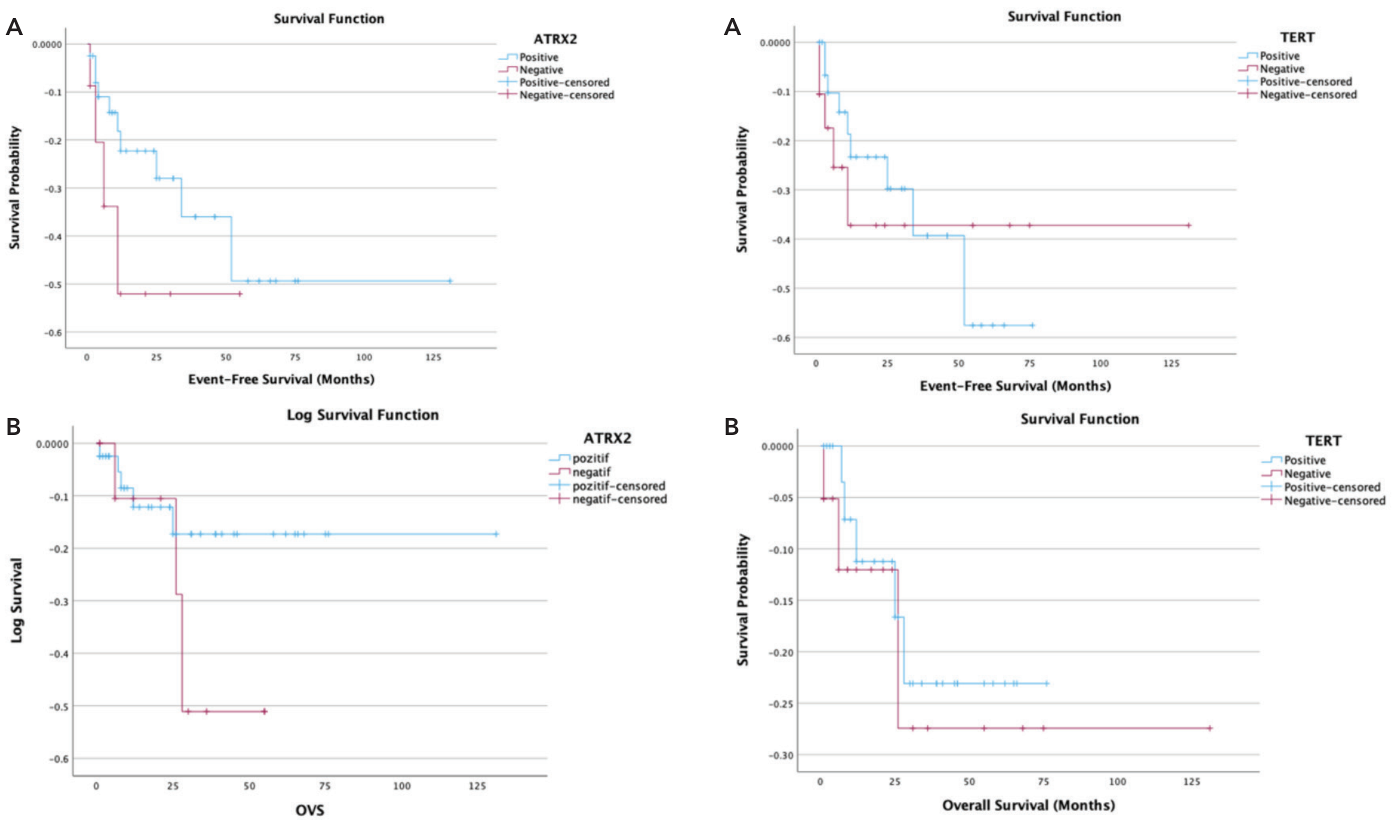

Figure 3. ATRX and TERT case plots showing overall survival (OS) and event-free survival (EFS) rates for neuroblastoma (NB)

ATRX- and TERT- positive and negative case plots for OS and EFS in NB patients. Kaplan-Meier curves showing ATRX- and TERT- positive and negative NB cases. OS (A) and EFS (B) of NB patients with ATRX and TERT- negative (red line) and ATRX- and TERT- positive (blue line) tumours are shown. Log-rank test was used to compare ATRX- and TERT- positive and negative NB cases.

ATRX: Alpha-thalassemia/mental retardation x-linked, TERT: Telomerase reverse transcriptase

have demonstrated poorer OS compared to children in Surveillance, Epidemiology, and End Results -based studies, even when detected earlier which suggests both stage of NB and biological differences as determinants of survival. Ten-year OS has been observed to decrease to around 19% in adult-onset NB series. In keeping with previous research, our findings in this study have also demonstrated a notable drop of 40% in OS rates in the group of children aged ≥5 years. The trend is similar, even though this figure is better than the rates indicated for adults and adolescents in the literature[25].

In NB, telomere length has been investigated as a significant prognostic indicator, with evidence indicating that shorter telomeres are associated with a more favourable clinical outcome, whereas longer or unchanged telomere lengths correlate with poorer prognoses[20]. More recently, activation of telomerase due to genomic rearrangements near the *TERT* gene locus has been identified in NB, delineating a subgroup of high-risk tumours characterized by exceptionally poor survival outcomes[13,26]. These investigations have demonstrated that *TERT* rearrangements are linked to elevated levels of *TERT* mRNA and enhanced telomerase enzymatic activity. In the study conducted by Lee et al.[20], *TERT* expression was assessed through IHC staining, revealing an inverse, but statistically insignificant association between *TERT* expression and patient survival. Similarly, in the current study, although a marked increase in *TERT* expression was observed in tissue samples of patients, still the inverse relationship with survival lacked statistical significance. Additionally, one of the earliest reports identifying *ATRX* involvement in NB revealed *ATRX* mutations in 44% of metastatic NB cases among adolescents and young adults, whereas such mutations were absent in tumour tissues obtained from infants with metastatic disease[23]. Children whose tumours harbored *ATRX* mutations were generally older than five years or exhibited a more indolent or chronic disease progression. In the same investigation, *ATRX* mutations were found to occur independently of *MYCN* amplification and were linked with nuclear loss of *ATRX* protein, telomere lengthening, and the activation of the alternative lengthening of telomeres (ALT) pathway[23]. Our findings also support this trend. Indeed OS was significantly worse in the ≥5 age group and remained an independent risk factor in the multivariate model, independent of age, *MYCN* status, and INRGSS risk group (HR: 3.2; 95% CI: 1.1-9.3; p=0.032). This result suggests that age acts as a higher-level marker that captures biological differences on the *ATRX*/*TERT* axis in addition to the classic risk classification.

Another study indicated that the majority of high-risk NB tumours exhibit either *TERT* rearrangements, *MYCN* amplification, or *ATRX* mutations —alterations that collectively promote telomere elongation and provide a molecular basis for defining this subtype of NB[26]. Conversely, low-risk tumours are typically devoid of these genomic alterations and exhibit low *TERT* expression, which may reflect an inability to achieve unlimited proliferative capacity. The most aggressive subtype of NB has been associated with telomerase activation resulting from either *TERT* rearrangements or *MYCN* amplification. With ongoing advances in telomerase inhibitor development, these findings may offer a promising therapeutic avenue for treating the most lethal forms of this paediatric malignancy. Furthermore, three recent reports have shown that *ATRX* mutations frequently cause loss of protein expression in NB and are more prevalent in older patients and those diagnosed with stage IV disease[23,27,28]. In our cohort, *MYCN* amplification was also found to be significantly associated with EFS and OS in multivariate analysis, consistent with the rekevant literature data. Since *ATRX* and *TERT* expressions per se fail to predict survival these biomarkers should be evaluated together with multiple parameters rather than independently in clinical practice.

Only 4 out of 53 patients (7.5%) in our dataset had both *MYCN* amplification and 11q deletion, indicating a trend of reciprocal exclusivity; however, this negative correlation was not statistically significant (p=0.145). This finding is directionally consistent with the well-established genomic landscape of NB, where these two alterations are known to rarely coincide and define distinct molecular subtypes demonstrating aggressive clinical behavior[29,30]. For instance, a comprehensive genomic study by Molenaar et al.[28] in 2012 on 87 NB cases found a strong pattern of mutual exclusivity between *MYCN* amplification and 11q loss, a hallmark that helps stratify high-risk disease. Similarly, the large-scale study performed by Pugh et al.[27] in 2013, which analyzed the genetic landscape of 240 high-risk NBs, confirmed that 11q deletion and *MYCN* amplification are significantly and mutually exclusive events (p<0.001), underscoring their roles in alternative pathways of oncogenesis. Limited sample size of our study compared to large cohort studies may reduce statistical power of our conclusions. Nevertheless, the very low frequency of co-occurrence observed among these parameters reinforces the concept that these are separate oncogenic drivers.

CONCLUSION

The present study revealed a relationship between expression levels of *ATRX* and *TERT* and both the NB risk classification and clinical prognosis. Interestingly, *ATRX* expression was found to be higher in NB patients, especially in those with *MYCN* amplification, suggesting its potential utility as an IHC prognostic marker. Considering their biological significance, *ATRX* and *TERT* emerge as important molecular candidates that may enhance our understanding of NB pathology. Nonetheless, their exact mechanisms of action in NB are yet to be fully elucidated. To clarify their roles, future research should be performed with larger patient cohorts and should focus on in-depth mechanistic investigations, supported by validation in clinical tissue samples.

Ethics

Ethics Committee Approval: Permission was obtained from Dokuz Eylül University (DEU) Non-Interventional Research Ethics Committee for the conduction of this research study (decision no: 2023/14-10, dated: 03.05.2023).

Informed Consent: Signed consent forms were obtained from the patients during the sample collection and storage stages.

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Footnotes

Author Contributions

Surgical and Medical Practices: M.T., S.K.Ö., D.K., S.A., Z.A., N.O., Concept: D.K., S.A., Z.A., T.Ç.A., E.Ö., N.O., Design: D.K., S.A., Z.A., T.Ç.A., E.Ö., N.O., Data Collection or Processing: M.T., S.K.Ö., G.S., D.K., S.A., Z.A., N.O., Analysis or Interpretation: M.T., S.K.Ö., G.S., S.A., Z.A., Literature Search: M.T., S.K.Ö., G.S., S.A., Z.A., Writing: M.T., S.K.Ö., G.S., N.O.

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Original Article

Digital Rights Access and Social Exclusion Dynamics of Children with Disabilities: A Mixed-Methods Study

Engelli Çocukların Dijital Haklara Erişimi ve Sosyal Dışlanma Dinamikleri: Karma Yöntemlerle Yapılmış Bir Araştırma

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ABSTRACT

Objective: This study aims to examine how structural, social, and economic inequalities influence the rights of children with disabilities to access, participate, and be protected in digital environments in Türkiye.

Method: A cross-sectional mixed-methods study design was adopted. The sample consisted of 82 children with disabilities aged 12-15 years living in İzmir, Türkiye. Quantitative data were collected using a Socio-Demographic Information Form, the Cyber Victimization Scale, and the Social Exclusion Scale for Children (SESC). Qualitative data were obtained through semi-structured interviews with 20 children and 15 parents. Quantitative data were analyzed using descriptive statistics, while qualitative data were analyzed through thematic content analysis.

Results: Most children owned a smartphone (88.6%), whereas 38.6% had a computer and 37.1% had a tablet; while 38.0% of households lacked fixed internet access. Among visually impaired children, 40.0% reported that screen readers were outdated, non-functional, or insufficient, whereas children with hearing impairments frequently reported a lack of subtitles. According to the SESC, 35.4% lacked financial access to healthcare services, 23.2% could not access safe housing, and 25.6% were unable to regularly participate in social activities. Online risks included receiving insulting (30.5%) or sexually explicit (8.5%) messages, offensive nicknames (24.4%), being mocked or excluded from games or chats (20.7%), unauthorized sharing of private content (17.1%). More than half (57.3%) of the children were unable to assess online information reliability, 21.4% were unaware of digital opportunities, and 32.1% had never produced digital content. Additionally, 52.4% of parents did not approve of their children sharing content on social media. Themes emerging from the qualitative analysis included access to digital technologies, digital development and literacy, disability-specific content, participation rights, experiences of digital rights violations, responsibilities, complaint mechanisms, and privacy and safety.

Conclusion: Digital access among children with disabilities is restricted by device, connectivity, and accessibility gaps; participation is constrained by material deprivation; and cyber risks remain prevalent. These findings highlight that digital participation is a multidimensional rights issue requiring strengthened digital literacy, standardized accessibility, and effective protection and reporting mechanisms.

Keywords: Disabled children, internet access, cyberbullying, digital divide

ÖZ

Amaç: Bu çalışma, Türkiye’de engelli çocukların dijital ortamlardaki erişim, katılım ve korunma haklarının yapısal, sosyal ve ekonomik eşitsizliklerden nasıl etkilendiğini incelemeyi amaçlamaktadır.

Yöntem: Kesitsel karma yöntem tasarımı kullanılmıştır. Örneklem, İzmir’de yaşayan 12-15 yaş arası 82 engelli çocuktan oluşmuştur. Nicel veriler Sosyodemografik Bilgi Formu, Siber Mağduriyet Ölçeği ve Çocuklar için Sosyal Dışlanma Ölçeği (SESC) ile; nitel veriler 20 çocuk ve 15 ebeveynle yapılan yarı yapılandırılmış görüşmelerle toplanmıştır. Nicel veriler tanımlayıcı istatistiklerle, nitel veriler tematik içerik analiziyle çözümlenmiştir.

Bulgular: Katılımcıların %88,6'sının akıllı telefonu bulunurken, %38,6'sının bilgisayarı ve %37,1'inin tableti vardır; hanelerin %38,0'ında sabit internet bulunmamaktadır. Görme engelli çocukların %40,0'ı ekran okuyucuların yetersiz/çalışmadığını; işitme engelli çocuklar sıklıkla altyazı eksikliğini bildirmiştir. SESC'ye göre sağlık hizmetlerine maddi erişimi olmayanlar %35,4; güvenli/konforlu konuta erişemeyenler %23,2; sosyal etkinliklere düzenli katılamayanlar %25,6'dır. Çevrimiçi riskler arasında hakaret içeren mesajlar (%30,5), aşağılayıcı lakaplar (%24,4), oyun/sohbetlerden alay edilme veya dışlanma (%20 ,7), özel içeriklerin izinsiz paylaşımı (%17,1) ve cinsel içerikli mesajlar (%8,5) öne çıkmaktadır. Çocukların %57,3'ü çevrimiçi bilginin güvenilirliğini ayırt edemediğini, %21,4'ü internet olanaklarından haberdar olmadığını, %32,1'i hiç dijital içerik üretmediğini bildirmiştir. Ebeveynlerin %52,4'ü çocuklarının sosyal medyada içerik paylaşmasını onaylamamıştır. Nitel bulgular; dijital teknolojilere erişim, dijital gelişim/okuryazarlık, engelliliğe özgü içerik, katılım hakları, hak ihlali deneyimleri, sorumluluklar, başvuru/şikayet mekanizmaları ve mahremiyet-güvenlik temalarını ortaya koymuştur.

Sonuç: Engelli çocuklarda dijital erişim cihaz–bağlantı–erişilebilirlik açıklarıyla sınırlanmakta; katılım maddi yoksunlukla daralmakta; korunmada siber riskler yaygın seyretmektedir. Bulgular, dijital katılımın çok boyutlu bir hak meselesi olduğunu doğrulamakta; dijital okuryazarlığın güçlendirilmesi, erişilebilirliğin standartlaştırılması ve etkili koruma/başvuru mekanizmalarının güvence altına alınması gereğine işaret etmektedir.

Anahtar kelimeler: Engelli çocuklar, internet erişimi, siber zorbalık, dijital uçurum

INTRODUCTION

Digitalization has profoundly reshaped the way the children play, learn, communicate, and express themselves. Children are no longer passive consumers of online content but active participants in digital spaces[1,2]. This transformation calls for a redefinition of children's rights in the digital era. Articles 12, 13, and 17 of the United Nations Convention on the Rights of the Child guarantee children's rights to express views, access information, and enjoy freedom of expression. General Comment No. 25 (2021) on children's rights reinforces that these rights apply equally in digital environments[3].

For children with disabilities, digital participation offers opportunities for inclusion and visibility. However, when accessibility is limited, these opportunities turn into risks of exclusion[4,5]. Accessibility is a multidimensional issue that goes beyond technology to encompass social, economic, and political factors. Assistive tools like screen readers, captions, or adaptive interfaces are essential but often insufficient or unavailable. Studies in Türkiye indicate that digital content rarely aligns with disability-specific needs, and public services lack consistent accessibility standards[4,5].

Digital inequality is shaped not only by technical factors but also by structural disadvantages such as poverty, parental education, and family digital literacy[6,7]. In low-income households, children often face limitations in accessing devices, stable internet connection, and digital educational resources. These disparities are amplified for children with disabilities, especially when intersecting with gender and geographic disadvantages. For instance, girls with disabilities in under-resourced areas may experience compounded forms of exclusion both online and offline.

This study investigates how structural, social, and economic inequalities negatively influence the rights of children with disabilities to access, participate, and be protected in digital environments in Türkiye. Using a mixed-methods approach, it explores digital exclusion as a form of structural inequality and aims to contribute to inclusive, rights-based digital policy discussions.

MATERIALS and METHODS

This study was designed using a mixed-methods approach to comprehensively examine the multidimensional inequalities faced by children with disabilities in digital environments. The research employed a cross-sectional, non-interventional, and single-center design, incorporating both quantitative and qualitative data collection techniques.

This study was approved by the Non-Interventional Ethics Committee of Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital (decision no.: 2025/01-07, dated: 09.01.2025). Informed written consent was obtained to ensure the voluntary participation of children and their families. Throughout the research process, principles of confidentiality, protection of personal data, and respect for children's rights to expression and representation in digital spaces were strictly observed. Surveys were conducted anonymously, and the data collected were used solely for academic analysis and advocacy purposes. Data collection procedures adhered to the principles outlined in UNICEF's Research Ethics in Evaluation (2021), the Declaration of Helsinki, and GDPR/KVKK regulations.

The study population consisted of 850 children with disabilities aged 12-15 years who applied to the Clinics of Outpatient Clinics of University of Health Sciences Türkiye, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital in 2024 Among them a total of 80 children who met the inclusion criteria and selected by simple random sampling method were enrolled in the study after they and their parents had given their voluntary consent.

The adequacy of the sample size was determined through an a priori power analysis, assuming a medium effect size (d=0.5), a level of statistical significance (p=0.05), and a statistical power of 0.80[8]. The analysis indicated that at least 60 participants would be sufficient; thus, the planned sample size consisting of 80 participants was considered adequate to ensure statistical reliability[8,9].

The Patients Who:

- Were between 12-15 years of age,
- Had an official disability report (visual, hearing, physical, or intellectual disability), with a minimum impairment level of 40% as required by national guidelines,
- Obtained written voluntary consent of their parents,
- Expressed their willingness to participate in the study consisted the study population.

Exclusion Criteria:

- Children with severe cognitive disabilities preventing effective communication,
- Lack of parental consent for participation.

Data were collected using the Sociodemographic Information Form, the Cyber Victimization Scale, and the Social Exclusion Scale for Children (SESC). For the qualitative strand data analysis, semi-structured interviews were conducted with 20 children and 15 parents. Data saturation was considered achieved at this point.

Sociodemographic Information Form

A Sociodemographic Information Form, developed by the researchers, was used to identify participants' background characteristics. The form included questions on children's age, gender, and type of disability, as well as parental education, occupation, and socioeconomic status. In addition, children's ownership of digital devices (smartphones, computers, tablets), the frequency of internet access, social media and online platform use were assessed which allowed for a systematic evaluation of the relationship between families' and children's digital access conditions and sociodemographic factors.

Cyber Victimization Scale

The Cyber Victimization Scale was developed by Arıcak et al.[10] to assess adolescents' experiences of victimization in online environments. The scale consists of 24 items, each one is responded dichotomously as "Yes" (2 points) or "No" (1 point). It has a unidimensional structure with no reverse-coded items. The total score ranges from 24 to 48, with higher scores indicating greater levels of cyber victimization. The scale demonstrated high internal consistency, with a Cronbach's alpha coefficient of 0.89.

SESC

The SESC was developed by Jiang et al.[11] to assess multidimensional social exclusion using a reliable and valid self-report measure. The adaptation and cultural-linguistic validation of the Turkish version of the scale were carried out by Karakaya et al.[12]. The SESC consists of 19 items rated on a 5-point Likert scale, each reflecting a different dimension of children's experiences of social exclusion. The Turkish adaptation studies confirmed that the scale is age-appropriate, practical, easy to administer, and psychometrically reliable[12].

Statistical Analysis

The data obtained in this study were analyzed using a mixed-methods approach that combined both quantitative and qualitative techniques. Quantitative data were analyzed using the IBM® Statistical Package for the Social Sciences (SPSS) software that employed descriptive statistical methods. Frequency distributions, percentages, and cross-tabulations were employed to determine general trends regarding children's access to digital tools, usage patterns, social media experiences, awareness of online safety, and exposure to digital risks. In addition, the effects of demographic variables such as gender, age, type of disability, and levels of parental education on children's digital experiences were examined in detail. These analyses revealed that digital inequality is shaped not only by technical infrastructure but also by broader social conditions.

Qualitative data were analyzed using thematic content analysis. The transcripts of semi-structured interviews were first subjected to open coding, after which the codes were clustered into thematic categories to construct an analytical framework. Four key themes emerged from this process: "barriers to access digital tools," "families' lack of digital literacy," "perceptions of online safety and privacy," and "limitations in freedom of expression and participation in digital spaces." Thus, the qualitative analysis deepened and contextualized the quantitative findings, providing a more comprehensive understanding of children's digital experiences.

RESULTS

The participating children had physical disabilities (n=40; 50.0%), visual (n=24; 29.3%) and hearing (n=17; 20.7%) impairments. The study population consisted mostly of boys (64.6%, n=53) rather than girls (35.4%,

Table 1. Demographic characteristics of children

Variable			n	%
Type of disability	Physical disability		41	50.0
	Physical disability		24	29.3
	Physical disability		17	20.7
Gender	Female		29	35.4
	Male		53	64.6
Mother's education	Literate only		14	17.3
	Primary school		33	40.7
	Secondary school		11	13.6
	High school		16	19.8
	University		7	8.6
Father's education	Literate only		10	12.2
	Primary school		21	25.6
	Secondary school		22	26.8
	High school		25	30.5
	University		4	4.9
Owned digital services	Smartphone		62	88.6
	Computer		27	38.6
	Tablet		26	37.1
	Min	**Max**	**Mean**	**SD**
Age (years)	8.00	18.00	13.23	1.98
Age of first digital exposure (years)	5.00	15.00	9.67	2.47

SD: Standard deviation

n=29). Regarding parental education levels, the majority of mothers were primary school graduates (40.7%, n= 33), with only 8.6% (n=7) of them holding a university degree. Fathers had slightly higher educational attainment, with 30.5% (n=25) of them graduating from high school. In terms of digital device ownership, smartphones were most frequently used digital device by the participants (88.6%, n=62), while computer (38.6%, n=27) and tablet (37.1%, n=26) ownership remained at a comparatively lower rate (Table 1).

Digital Access Problems by Type of Disability

At least 40.0% (n=10) of visually impaired children reported that their screen reader software did not work, was outdated, or inadequate in Turkish content. Hearing-impaired children reported that they were receiving unpleasant (n=2; 12.2%) or insulting messages (n=2; 9.8%), and being mocked (n=1; 8.5%), and threatened (n=1; 4.9%) (Figure 1).

Spatial and Socioeconomic Context

A total of 31 (38.0%) participants reported that they did not have a fixed internet connection at home and could only access the internet using their parents' mobile data.

Among parents, only 7 (8.6%) mothers and 4 fathers (4.9%) were university graduates. Based on the responses given to the items of The SESC, 35.4% (n=29) of participants reported that their families did not have sufficient financial means to access medical services, 23.2% (n=19) could

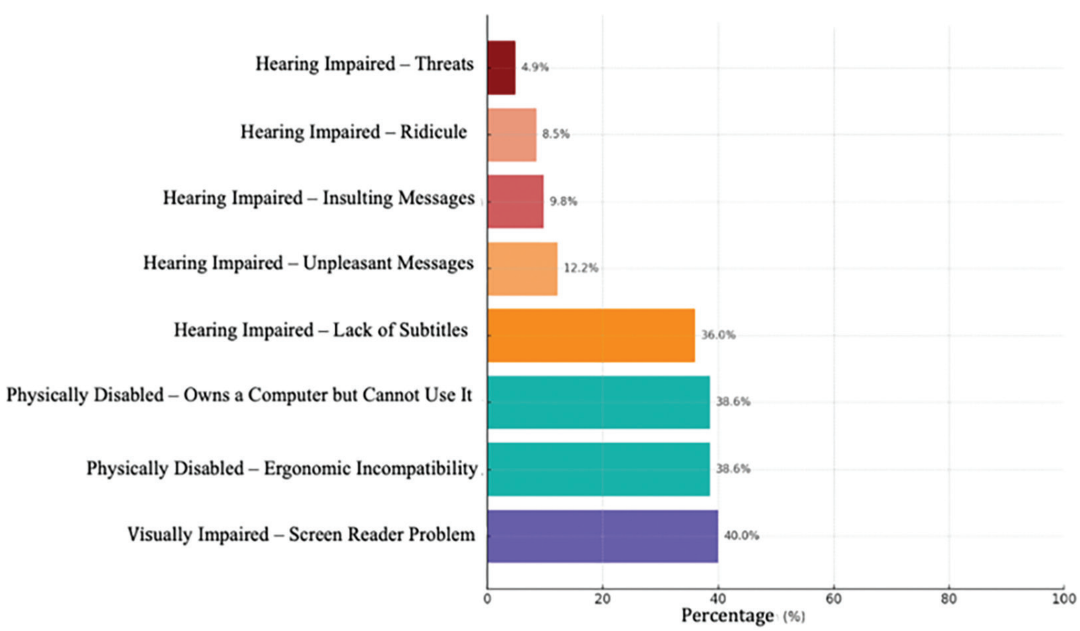

Figure 1. Digital access and safety issues by disability type

not afford to live in a safe and comfortable home, and 25.6% (n=19) were unable to participate regularly in social activities (Figure 2).

Digital Literacy and Information Accessibility

The indicated number (%) of study participants reported that they could not determine the reliability of information on the internet (n=47; 57.3%), had never produced digital content (n=26;32.1%), and were not aware of the opportunities provided by the internet (n=18; 21.4%),

Additionally, they reported that they had received insulting (n=25;30.5%) or sexually explicit (n=7; 8.5%) messages, had been called by offensive nicknames (n=20;24.4%), and their private photos or videos were shared without permission (n=7;8.5%) (Figure 3).

Safety and Digital Violence Experiences

The study participants also reported that they had received insulting (n=25; 30.5%) or sexually explicit (n=14; 17.1%) messages, had been called by offensive nicknames (n=20; 24.4%) or mocked or excluded from games, chats, or social groups (n=17; 20.7), and their

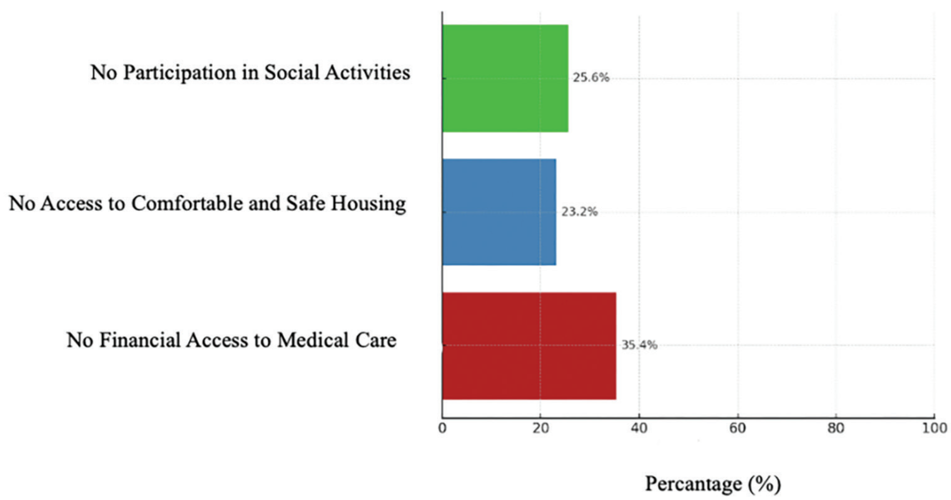

Figure 2. Indicators of social exclusion among children with disabilities

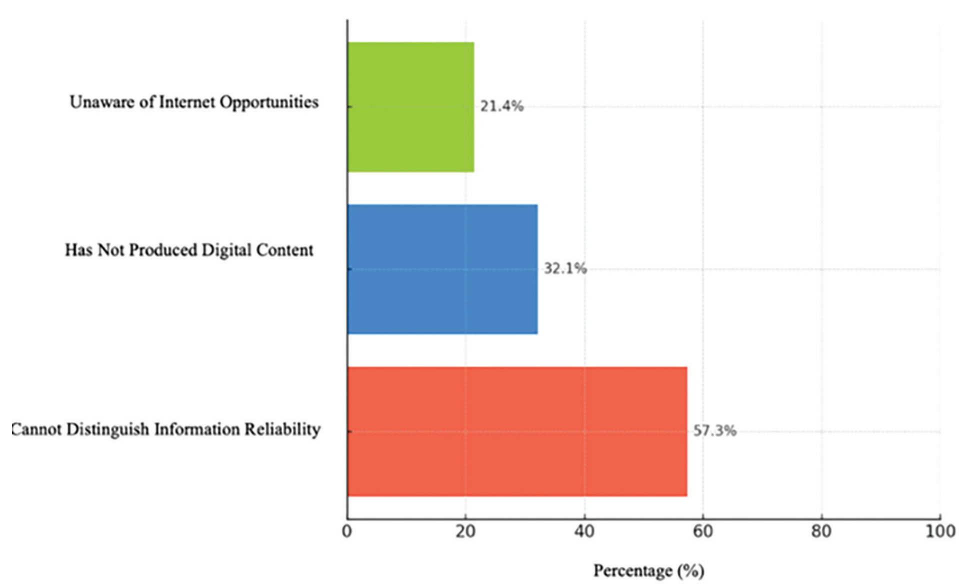

Figure 3. Limitations in digital literacy among children with disabilities

private photos or videos had been shared without permission (n=14; 17.1%).

The majority of children stated that they did not report these experiences to any complaint mechanism (Figure 4).

Right to Participation and Visibility

A total of 15 (18.3%) children reported that they had produced digital content. Additionally, they stated that they had not received any support regarding freedom of expression online (n=26; 32.1%), felt unsafe when sharing their opinions (n=34; 41.5%), experienced excessive parental control (n=24; 29.3%), and faced bullying when expressing their views (n=18; 21.9%). Finally, 43 (52.4%) parents reported that they had not approved of their children sharing content on social media (Figure 5).

Qualitative Findings

The qualitative interviews revealed eight main themes: (1) access to digital technologies, (2) the right to digital development and digital literacy, (3) access to content tailored to specific needs, (4) participation rights in digital environments, (5) experiences of digital rights violations, (6) responsibilities in digital environments, (7) defense mechanisms against rights violations, and (8) perceptions of privacy and security rights.

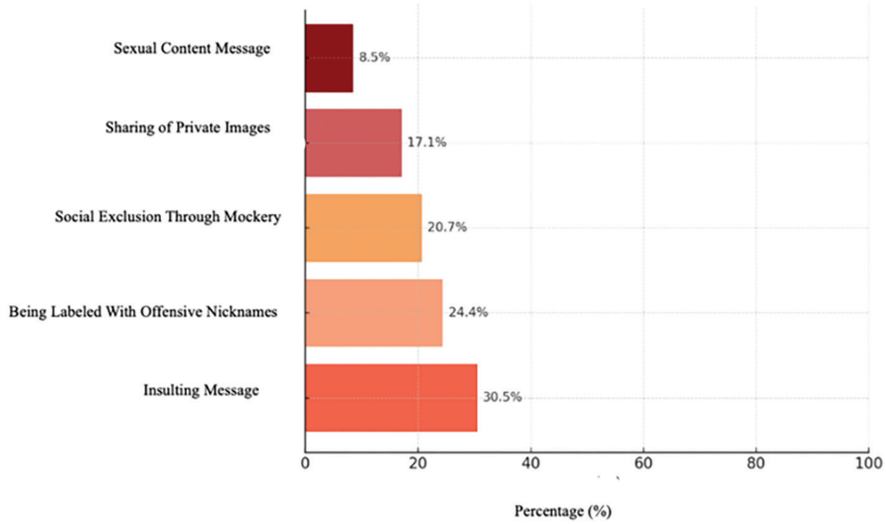

Figure 4. Rights violations in digital environments among children with disabilities

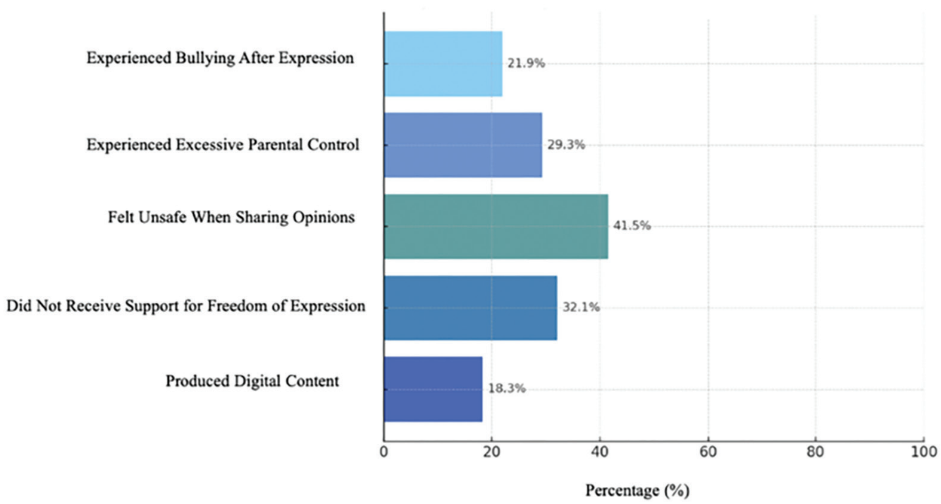

Figure 5. Experiences of digital participation and freedom of expression among children with disabilities

Theme 1: Access to Digital Technologies

Participants reported difficulties in accessing and using devices depending on their type of disability. Visually impaired children emphasized the malfunction or inadequacy of screen readers, physically disabled children mentioned challenges with keyboards, mice, and touchscreens, and hearing-impaired children reported the lack of subtitles and sign language support. High costs of special devices, limited internet access, and difficulties communicating needs to families were also mentioned.

- "It is hard for me to access digital technologies because I need special tools like a screen reader. But these tools sometimes do not work properly." (C1, visually impaired, age 13).
- "I have a phone, but using a touchscreen is difficult for me. A phone with larger buttons would be better." (C4, physically disabled, age 12).
- "We have an old computer that barely works…using the keyboard or the mouse is really hard." (C8, physically disabled, age 13).

Theme 2: Right to Digital Development and Digital Literacy

Children expressed challenges in exercising their rights to digital development due to lack of knowledge, insufficient programs, and access barriers. They indicated a desire to improve digital literacy but noted difficulties in staying safe online and identifying reliable information.

- "Digital literacy teaches me how to find the right information and stay safe online. I want to learn more about this." (C2, visually impaired, age 12).
- "I want to develop myself in the digital world like everyone else, but it is hard when I don't understand how everything works." (C5, physically disabled, age 14).

Theme 3: Access to Content Tailored to Specific Needs

Participants reported limited access to educational materials suitable for their disabilities, noting that existing content was scarce or not engaging.

- "My access to special educational materials is very limited." (C1, visually impaired, age 13).
- "There are audio books and screen readers, but they are not interesting enough, and games are very few." (C2, visually impaired, age 12).
- "It is difficult to find content designed for children like me. I want to access more." (C4, physically disabled, age 12).

Theme 4: Participation Rights in Digital Environments

Children described restrictions in community-building and participation, with accessibility gaps and fear of bullying as major issues.

- "Children with disabilities hide their identities because of the fear of exclusion… we are also afraid of being bullied in digital life." (C2, visually impaired, age 12).
- "There should be online platforms where children with disabilities can talk and play together." (C4, physically disabled, age 12).
- "Since people cannot hear me online, I get excluded from chats and games." (C7, hearing impaired, age 13).

Theme 5: Experiences of Digital Rights Violations

Participants reported facing harassment, discrimination, and mockery online, along with accessibility issues. These experiences were often associated with sadness and withdrawal.

- "Once while playing a game online, a group of kids teased me and made fun of me. I blocked them, but I still felt upset." (C3, hearing impaired, age 14).
- "When I was playing a game, other kids mocked me. I felt bad and left the game." (C4, physically disabled, age 12).
- "Sometimes I feel excluded or ignored online because of my disability." (C8, physically disabled, age 13).

Theme 6: Responsibilities in Digital Environments

Children stated that individuals should behave respectfully, institutions should provide inclusive programs and safe content, and developers should design accessible games and websites.

- "The state and internet companies should create programs and content for children with disabilities." (C3, hearing impaired, age 14).
- "There should be laws and regulations to make it easier for children with disabilities to access their rights." (C4, physically disabled, age 12).
- "Websites and games should work for everyone. This is not just about being kind; it is about equal treatment." (C8, physically disabled, age 13).

Theme 7: Defense Mechanisms Against Rights Violations

Most participants reported not knowing where to file complaints, while some mentioned asking teachers or parents for help. The need for complaint hotlines and support systems was highlighted.

- "I don't report problems to anyone because I don't know where to apply." (C1, visually impaired, age 13).
- "I don't know where to apply. It is important to have resources that provide support." (C5, physically disabled, age 14).
- "If something bad happens online, I think I could talk to my parents or teacher." (C7, hearing impaired, age 13).

Theme 8: Privacy and Security Rights

Participants highlighted the need to protect personal information, safe use of the internet, and be taught clearer rules.

- "I don't share my personal information much, but I don't know who gets it." (C2, visually impaired, age 12).
- "I don't know how my information is used online. I wish someone could teach me how to stay safe." (C3, hearing impaired, age 14).
- "I don't always know how to protect myself online… there should be clearer rules or guidelines." (C7, hearing impaired, age 13).

DISCUSSION

Children's experiences with digital technologies should be understood not only as individual usage patterns but as processes through which broader social inequalities are reproduced online. In this study, children with disabilities encountered predominantly interpersonal conduct harms (e.g., insulting messages, name-calling, exclusion) rather than purely content-based threats, aligning with digital inequality frameworks and Livingstone and Helsper's[13] and Livingstone's[14] 4Cs model that classifies online risks exposed by children at the intersection of content, contact, conduct, and commercial factors. Interpreting our mixed-methods evidence together suggests that limited accessibility features, constrained device/connectivity conditions, and low parental digital literacy converge to limited safe participation and increase vulnerability to peer-to-peer harms.

These patterns are consistent with comparative European findings showing that cyberbullying and social exclusion remain the most frequent online risks[15] together with work documenting the psychosocial toll of online aggression[16]. The relatively lower cyberbullying levels observed in our sample vis-à-vis multinational European Union Kids Online research network may reflect more passive digital participation (e.g., limited content production), which can reduce exposure to privacy violations without fully mitigating conduct-related harms. Such variation also likely reflects contextual differences in parental mediation and platform practices across diverse settings.

Children's first-hand reports of malfunctioning screen readers, absent captions/sign language, and inadequate assistive tools mirror international evidence linking weak accessibility standards to exclusion from learning and social life[17,18]. Our findings extend this literature by showing how everyday accessibility gaps interact with poverty and limited parental digital competence to shape risk exposure and self-censorship.

Socioeconomic and familial constraints further structure digital opportunity. Low parental education and limited household resources were salient, consistent with research showing that socioeconomic status and parental digital competence shape inclusion trajectories[19,20]. In our context, modest parental educational attainment likely weakens protective mediation, reinforcing disadvantage despite children's motivation to engage.

Qualitative accounts illuminated the emotional mechanisms linking exclusion and participation ie. ridicule, fear, and withdrawal curtailed expression and visibility, while restrictive parental norms including disapproval of children's sharing aggravated sociocultural constraints[21,22]. Children also articulated clear expectations for protective structures (accessible reporting channels, inclusive platform design, enforceable rules), underscoring that online safety requires both individual competencies and assistive institutional infrastructures[23].

Overall, the convergence of quantitative and qualitative strands indicates that children with disabilities are disproportionately exposed to multidimensional risks while being excluded from the benefits of meaningful participation. We argue that digital participation for this group is fundamentally an equity and rights issue requiring universal design, accessible content/services, strengthened digital literacy for families and educators, and child-centred governance that ensures effective and usable redress mechanisms.

Methodological note: Because disability types were heterogeneous and subgroup sizes were limited and unequal, we did not conduct inferential comparisons across groups and reported descriptive patterns only (see Limitations). Future studies should use stratified recruitment, a priori power for subgroup analyses, and multilevel/stratified models to better account for heterogeneity.

Strengths of the Research

One of the key strengths of this study is the adoption of a dual analysis strategy, whereby general trends identified through quantitative data were integrated with individual narratives. This approach enabled both a structured and also flexible level of interpretation, consistent with the theoretical foundations of the study. Moreover, by framing children as active subjects rather than passive respondents, the analysis emphasized not merely representational but also transformative characteristics of data. This perspective contributed favorably to both ethical and methodological originality of our research.

Study Limitations

Despite its carefully designed mixed-methods strategy, this study has certain limitations. Firstly, national generalizability of this research is limited because fieldwork was conducted exclusively in İzmir, and the findings are context-specific and may not fully represent children with disabilities across Türkiye. Second, although diversity in disability types was considered at sampling, sizes of subgroups (e.g., physical, visual, and hearing) were small and unequal, introducing heterogeneity that may influence device access, accessibility needs, digital literacy, and exposure to online risks. We therefore refrained from making inferences between-group comparisons and reported descriptive patterns only (see Figure 1), which should be borne in mind when interpreting differences across disability types. In addition, certain populations particularly children with intellectual disabilities, pervasive developmental disorders, or neurodiverse profiles were under-represented, narrowing the scope of insights into their digital experiences. Future studies should employ stratified recruitment, a priori power calculations for subgroup comparisons, and multilevel or stratified analytic models to better account for heterogeneity.

CONCLUSION

This study shows that device access alone does not ensure meaningful, safe, and equitable digital participation for children with disabilities. Evidence from both methods indicates that structural barriers (insufficient accessibility features, low parental digital literacy, and socio-economic disadvantage) limit children's ability to benefit from digital opportunities with persistence of psychosocial risks (cyberbullying, privacy breaches, social exclusion). Digital inequality is patterned by place and poverty, with disadvantaged districts facing greater risks due to weak infrastructure and limited guidance. These results call for rights-based, inclusive, and sustainable policies that mainstream universal design, build robust protections against digital violence, and strengthen digital literacy among children, families, and educators, alongside with targeted infrastructure investments and child participation in policymaking. Overall, digital participation for children with disabilities should be treated as an equity and rights issue. Future research should employ longitudinal and comparative designs to assess structural interventions.

Ethics

Ethics Committee Approval: This study was approved by the Non-Interventional Ethics Committee of University of Health Sciences Türkiye, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital with decision numbered 2025/01-07, dated 09.01.2025.

Informed Consent: Informed written consent was obtained to ensure the voluntary participation of children and their families.

Footnotes

Author Contributions

Concept: E.G. D.O., Z.İ.P.B., Design: E.G. D.O., Z.İ.P.B., Data Collection or Processing: E.G., Z.İ.P.B., Analysis or Interpretation: E.G., S.G., Literature Search: E.G., D.O., Z.İ.P.B., B.G. Writing: D.O., E.G., Z.İ.P.B., B.G.

Conflict of Interest: The authors have no conflict of interest to declare.

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Original Article

Sleep Disturbances and Internet Overuse in Pediatric Migraine: A Neuropsychiatric Approach

Pediatrik Migrenlerde Uyku Bozuklukları ve Aşırı İnternet Kullanımı: Nöropsikiyatrik Bir Yaklaşım

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ABSTRACT

Objective: The aim of this study was to evaluate sleep quality and internet use behaviours in children with pediatric migraine, focusing on their associations with anxiety, internet gaming disorder (IGD), and daytime functional impairment.

Method: The study included 38 pediatric patients aged 10-18 years with migraine and 35 age-matched controls without migraine or psychiatric complaints. Migraine characteristics were systematically assessed, and sociodemographic data were collected. Comorbid psychiatric symptoms were evaluated using the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version. All participants completed the Pittsburgh Sleep Quality Index (PSQI), the IGD Scale-Short-Form (IGDS9-SF), and the Screen for Child Anxiety Related Disorders (SCARED).

Results: The migraine patients comprised 65.8% females and 34.2% males. Of these, 26 reported a positive family history of migraine, 12 were diagnosed with migraine with aura, and 26 without aura. The SCARED and IGDS9-SF scores were significantly higher in the migraine group than in the control group (p=0.001, p=0.011). Total PSQI scores indicated poorer sleep quality in migraine patients (p=0.001). Sleep latency (p=0.579) and duration (p=0.882) did not differ between the groups but subscale analyses revealed significant impairments in subjective sleep quality (p=0.001), daytime dysfunction (p=0.018), sleep disturbances (p=0.001), and habitual sleep efficiency (p=0.001) in the migraine patients.

Conclusion: Pediatric migraine is associated with heightened anxiety, problematic gaming, and impaired sleep quality, contributing to daytime dysfunction. These results underscore the importance of a multidisciplinary approach addressing both migraine symptoms and co-existing psychological factors.

Keywords: Migraine, child and adolescent psychiatry, internet addiction, sleep quality

ÖZ

Amaç: Bu çalışmanın amacı, pediatrik migren tanılı çocuklarda uyku kalitesi ve internet kullanım davranışlarını değerlendirmek ve bu değişkenlerin anksiyete, internet oyun bozukluğu ve gündüz işlevselliği ile ilişkilerini incelemektir.

Yöntem: Çalışmaya, 10-18 yaş aralığında migren tanısı almış 38 çocuk ile migren veya psikiyatrik yakınması bulunmayan, yaş ve cinsiyet açısından eşleştirilmiş 35 sağlıklı kontrol grubu dahil edilmiştir. Migren özellikleri ve sosyodemografik veriler sistematik olarak kaydedilmiştir. Eşlik eden psikiyatrik belirtiler Çocuklar için Duygudurum Bozuklukları ve Şizofreni Tarama Çizelgesi-Şimdiki ve Yaşam Boyu Versiyonu ile değerlendirilmiştir. Katılımcılara Pittsburgh Uyku Kalitesi İndeksi (PUKİ), İnternet Oyun Bozukluğu Ölçeği-Kısa Form (İOOBÖ9-KF) ve Çocuklarda Anksiyeteye İlişkin Bozuklukları Tarama Ölçeği (ÇATÖ) uygulanmıştır.

Bulgular: Migren grubunun %65,8'i kız olup 26'sında ailede migren öyküsü mevcuttu. On iki olguda auralı, 26 olguda aurasız migren saptanmıştır. Migren grubunda ÇATÖ puanları kontrol grubuna göre anlamlı düzeyde yüksek bulunmuştur (p=0,001). İOOBÖ9-KF puanları da migren grubunda daha yüksektir (p=0,011). Toplam PUKİ puanları, migrenli çocuklarda daha düşük uyku kalitesine işaret etmiştir (p=0,001).

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Uyku latensi (p=0,579) ve süresi (p=0,882) açısından fark saptanmamıştır. Ancak öznel uyku kalitesi (p=0,001), gündüz işlev bozukluğu (p=0,018), uyku bozuklukları (p=0,001) ve alışılmış uyku etkinliği (p=0,001) alt ölçeklerinde anlamlı bozulma belirlenmiştir.

Sonuç: Pediatrik migren, artmış anksiyete düzeyi, problemli oyun oynama davranışı ve bozulmuş uyku kalitesi ile ilişkilidir. Bu bulgular, migrenin yönetiminde psikolojik eş tanıların dikkate alındığı multidisipliner yaklaşımların gerekliliğini vurgulamaktadır.

Anahtar kelimeler: Migren, çocuk ve ergen psikiyatrisi, internet oyun bozukluğu, uyku kalitesi

INTRODUCTION

Migraine is a common neurological disorder during childhood and adolescence that significantly impacts quality of life. Its etiology is thought to result from the interaction of genetic, environmental, and lifestyle factors[1]. The prevalence of migraine in childhood is approximately 10%, increasing to as high as 15% during adolescence[2,3]. Pediatric migraine is not limited to physical symptoms but also adversely affects cognitive, social, and emotional development. Studies have reported higher levels of depression and anxiety in children with migraine, together with increased school absenteeism, social withdrawal, and a marked decline in quality of life[4].

Recently, the increasing use of digital media has introduced new risk factors for migraine. Prolonged screen exposure has been associated with increased frequency and severity of migraine attacks, particularly when digital media is used during night-time hours[5]. Internet and gaming addiction may trigger migraine through mechanisms such as sleep disturbances, physical inactivity, and increased psychosocial stress[6]. Furthermore, Internet use has been reported to be associated with psychiatric symptoms. In a study examining adolescents diagnosed with migraine, those who used the Internet for more than two hours per week exhibited impairments in mood and social functioning[7].

Migraine is also bidirectionally associated with sleep disorders and psychiatric conditions. While poor sleep quality can increase the frequency of migraine attacks, headaches themselves may disrupt sleep patterns[8,9]. Sleep problems can lead to daytime sleepiness, impaired attention, and functional decline[10]. Previous studies have demonstrated a reduction in rapid eye movement (REM) sleep and disruption of sleep continuity in adult migraine patients[11]. It has also been reported that individuals with migraine experience increased daytime sleepiness, which negatively impacts daily functioning[12].

Psychiatric comorbidities such as anxiety, depression, attention deficit hyperactivity disorder (ADHD), and somatization are common in children and adolescents with migraine, complicating both diagnosis and treatment processes[13,14]. Migraine is considered not merely a headache disorder, but a multidisciplinary condition influenced by psychiatric, behavioral, and environmental factors[15]. In this context, the aim of this study was to assess the relationships between internet use, sleep quality, and psychiatric symptoms in children and adolescents diagnosed with migraine.

MATERIALS and METHODS

Participants and Study Design

The study included 38 children aged 10 to 18 years who were diagnosed with migraine, together with their parents, who presented at the Pediatric Neurology Clinic over a period of 2 months. The migraine diagnosis was made according to the criteria outlined in the third edition of the International Classification of Headache Disorders[16]. The study participants were categorized into two groups based on migraine subtype: those with aura and those without aura. Various factors, including the location, frequency, duration of headaches, and accompanying migraine symptoms were evaluated in detail and categorized. Parents were interviewed to offer opinions about the familial and emotional aspects related to managing their child's condition. A standardized pain scale was administered to all patients to evaluate headache severity, which was subsequently classified into three categories of mild, moderate, and severe[17].

All the study participants were referred to the child psychiatry clinic, with their parents, and were personally interviewed by the researcher. To identify comorbid psychiatric disorders and enhance diagnostic reliability, assessments were conducted using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL). All the participants were also asked to complete the Pittsburgh Sleep Quality Index (PSQI) to evaluate sleep quality, the Internet Gaming Disorder Scale-Short Form (IGDS9-SF) to assess problematic online gaming behaviours, and the Screen for Child Anxiety Related Emotional Disorders (SCARED) to measure anxiety levels.

A control group was formed of 35 children and their parents who did not present with any neurological or psychiatric complaints. The study exclusion criteria were defined as a dignosis of any chronic neurological disorder other than migraine, a clinical diagnosis of intellectual disability or autism spectrum disorder, and unwillingness to participate in the study.

Approval for this study was granted by the Non-Interventional Research Ethics Committee of the University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital (approval number: 2025/05-16, dated: 12.06.2025). Written and verbal informed consent was obtained from the participating children and their parents.

Instruments

Sociodemographic Data Form

This form was developed by the researcher based on a review of the literature and was completed by the researcher using information obtained from the parents. It includes sociodemographic and clinical characteristics related to the participant and their family. Specifically, the form collects data on the participant's age, sex, presence of perinatal complications, family history of migraine diagnosis, diagnosis, headache location, duration and frequency, whether the pain is unilateral or bilateral, presence of accompanying photophobia or phonophobia, presence of accompanying nausea or vomiting, headache severity, whether the headache is exacerbated by physical activity, presence of aura, and if present, the duration and type of aura. It also records whether the participant uses analgesic medications during attacks or prophylactically.

K-SADS-PL

This form is used to evaluate lifetime comorbid psychopathologies in children. If diagnostic symptoms are identified during the initial interview, an additional evaluation checklist is administered. The presence and severity of positive findings are determined based on the clinician's, family's, and participant's input. The standardization of the form has been conducted for Turkish children[18,19].

PSQI

The scale was developed by Buysse et al.[20] to assess sleep quality. The PSQI comprises seven components: sleep latency, sleep duration, subjective sleep quality, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. The total score ranges from 0 to 21 points, with 0-4 points indicating good sleep quality, and 5-12 points, poor sleep quality. The Turkish validity and reliability study of the scale was conducted by Yücel Ağargün et al.[21].

IGDS9-SF

This scale was developed by Pontes and Griffiths[22], based on nine core criteria that define IGD. These criteria can be summarized as follows: preoccupation with gaming, withdrawal symptoms, development of tolerance, unsuccessful attempts to control gaming behaviour, loss of interest in previous enjoyable activities, continued excessive gaming despite negative psychosocial consequences, deceiving family members or therapists regarding the amount of time spent gaming, using gaming to escape negative mood states, and jeopardizing or losing a significant relationship, job, educational, or career opportunity due to gaming. The Turkish validity and reliability study of the scale has been conducted[23].

SCARED

This scale was developed by Birmaher et al.[24] to screen for childhood anxiety disorders, and the Turkish validity and reliability study was conducted by Karaceylan Çakmakçı et al.[25] The scale consists of a total of 41 items, with scores of ≥25 points considered indicative of potential anxiety disorders.

Statistical Analysis

Data were analyzed using SPSS software. The Shapiro-Wilk test was used to assess the normality of data distribution. Variables with normal distribution were presented as mean ± standard deviation values, and variables not showing normal distribution as median and interquartile range values. Categorical variables were compared using the chi-square test or Fisher's exact test. Continuous variables were analyzed using the Independent Samples t-test or Mann-Whitney U test for two-group comparisons. Post-hoc tests were applied when significant differences were detected. A value of $p<0.05$ was considered statistically significant.

RESULTS

Evaluations were made of a total of 73 children, comprising 38 patients in the migraine group and 35 individuals in the control group. The mean age of the children was 13.6±2.5 year in the migraine group and 12.7±0.6 years in the control group, with no significant difference in age at presentation between the groups. Of the patients diagnosed with migraine, 65.8% (n=25) were female and 34.2% (n=13) were male; in the control group, 40% (n=14) were female and 60% (n=21) were male. A statistically significant difference in sex distribution was observed between the groups (p=0.027). A family history of migraine was reported in 68.4% (n=26) of the case group and in 14.3% (n=5) of the control group, with this difference also reaching statistical significance (p=0.001) (Table 1).

When clinical subtypes of migraine were evaluated, 12 patients were diagnosed with migraine with aura, and 26 patients with migraine without aura. According to the classification based on headache localization, pain was reported in the frontal region in 20 patients, parietal region in 3 patients, occipital region in 5 patients, and temporal region in 10 patients. Regarding lateralization, 11 patients experienced unilateral headaches, whereas 27 patients had bilateral headaches. Photophobia was observed in 29 patients, and phonophobia in 25 patients. Nausea was reported in 23 patients, and vomiting in 5 patients. When headache severity was assessed using a pain scale, 20 patients described their pain as severe, and 18 as moderate. Headaches triggered by physical activity were reported by 23 patients. Among those diagnosed with migraine with aura, 8 patients experienced visual aura symptoms, 2 somatosensory, and 2 auditory aura symptoms. According to the headache frequency classification, 4 patients reported headaches at least once a month, 19 at least once a week, 6 experienced headaches on average three days per week, and 9 reported daily headaches.

Table 1. Demographic and clinical characteristics of the cases

	Migraine group (n=38)	Control group (n=35)	p-value
Age (years)	13.6±2.5	12.7±0.6	0.057
Gender			0.027
Female	25 (65.8%)	14 (40%)	
Male	13 (34.2%)	21 (60%)	
Family history of migraine			0.001
Yes	26 (68.4%)	5 (14.3%)	
No	12 (31.6%)	30 (85.7%)	
Psychiatric diagnosis			<0.001
Yes	26 (68.4%)	8 (22.9%)	
No	12 (31.6%)	27 (77.1%)	
Anxiety disorder			0.001
Yes	25 (65.8%)	7 (20%)	
No	13 (34.2%)	28 (80%)	
Depressive disorder			0.201
Yes	5 (13.2%)	1 (2.9%)	
No	33 (86.8%)	34 (97.1%)	
OCD			0.241
Yes	3 (7.9%)	0 (0%)	
No	35 (92.1%)	35 (100%)	
ADHD			0.858
Yes	6 (15.8%)	5 (14.3%)	
No	32 (84.2%)	30 (85.7%)	

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

A significant difference was observed between the groups in respect of psychiatric diagnoses (p<0.001). Anxiety disorder was present in 65.8% (n=25) of the migraine group, compared to 20% (n=7) in the control group, with this difference reaching statistical significance (p=0.001). Of the patients with migraine, 13.2% (n=5) had comorbid depressive disorder, 7.9% (n=3) had obsessive-compulsive disorder, and 15.8% (n=6) had ADHD. In the control group, depressive disorder was present in 2.9% (n=1), and ADHD in 14.3% (n=5). No significant differences were found between the groups for these diagnoses (Table 1).

In the assessment of anxiety symptoms, the total score of the SCARED, was statistically significantly higher in the migraine group at 29.5±13.6 compared to 11.7±4.7 in the control group (p=0.001). The total score of the IGDS9-SF was 15.6±5.7 in the migraine group and 12.7±3.3 in the control group, showing a statistically significant difference (p=0.011). The total PSQI score was 6.7±3.7 in the migraine group and 3.7±2.1 in the control group, with a significant difference between groups (p=0.001). No significant differences were found between the groups in the PSQI sub-scores for sleep latency (0.8±0.86 vs. 0.9±0.7; p=0.579), sleep duration (0.7±0.9 vs. 0.7±0.6; p=0.882), and use of sleep medication (0.4±0.8 vs. 0.3±0.5; p=0.721). The sleep quality sub-score was significantly higher in the migraine group (1.3±0.9) compared to the control group (0.3±0.6) (p=0.001). The sub-scores for daytime dysfunction (1.0±1.1 vs. 0.5±0.6; p=0.018), sleep disturbances (1.4±1.0 vs. 0.6±0.7; p=0.001), and habitual sleep efficiency (1.4±0.8 vs. 0.4±0.6; p=0.001) were significantly higher in the migraine group than in the control group (Table 2).

DISCUSSION

The aim of this study was to comprehensively evaluate comorbid psychiatric symptoms, anxiety levels, sleep quality, and the tendency toward IGD in children and adolescents diagnosed with migraine. The findings

Table 2. Scale scores			
	Migraine group (n=38) Median (min-max)	Control group (n=35) Median (min-max)	p-value
SCARED total score	29.5±13.6	11.7±4.7	0.001
IGDS9-SF total score	156±5.7	12.7±3.3	0.011
PSQI total score	6.7±3.7	3.7±2.1	0.001
Sleep latency	0.8±0.86	0.9±0.7	0.579
Sleep duration	0.7±0.9	0.7±0.6	0.882
Sleep quality	1.3±0.9	0.3±0.6	0.001
Use of sleep medication	0.4±0.8	0.3±0.5	0.721
Daytime dysfunction	1±1.1	0.5±0.6	0.018
Sleep disturbances habitual	1.4±1	0.6±0.7	0.001
Sleep efficiency	1.4±0.8	0.4±0.6	0.001

SCARED: Screen for Child Anxiety Related Emotional Disorders, IGDS9-SF: Internet Gaming Disorder Scale-Short Form, PSQI: Pittsburgh Sleep Quality Index

indicated that migraine is not merely a neurological disorder but also constitutes a complex clinical condition that significantly affects psychosocial functioning.

Although migraine is defined as a neurovascular disorder, it has also long been investigated within a psychosocial framework. The current study finding of a higher prevalence of a family history of migraine compared to the control group supports genetic studies in the field that explore etiological factors[26]. However, in recent years, psychiatric factors have also been highlighted as both predisposing and perpetuating contributors. It is known that anxiety disorders are observed in 20-50% of children diagnosed with migraine[27]. Consistent with the literature, the current study observed a predominance of female sex among children with migraine, and anxiety rates were significantly higher compared to the control subjects. Notably, although a substantial proportion of the control group also exhibited anxiety or depressive symptoms (7 of 35 with an anxiety disorder, 1 with depression), the rates in the migraine group remained significantly elevated. This suggests that while psychiatric symptoms can occur in the general pediatric population, migraine may act as an independent risk factor for increased anxiety, potentially due to the unpredictable, chronic, and recurrent nature of attacks. The observed sex difference is most likely influenced by hormonal changes in addition to genetic and psychosocial factors[28]. The finding of increased anxiety symptoms in the migraine group is consistent with previous studies, which have stated that the unpredictable, chronic, and recurrent nature of migraine may elevate anxiety levels in children or have suggested that anxiety, by increasing the frequency of migraine attacks, acts as both a trigger and a secondary comorbid condition[29].

However, in the current study, no significant differences were observed in terms of comorbid depression and ADHD diagnoses. Although some studies have reported a strong association between migraine and these disorders[13], this relationship appears to vary particularly across clinical settings and age groups. Factors such as the sample size, the age range of participants, or the assessment methods employed in the current study may have limited the early detection of these disorders. Furthermore, considering the role of psychosocial factors in the etiology of migraine, it can be hypothesized that anxiety emerges earlier and more prominently in children with migraine, whereas disorders such as depression and ADHD may develop later or follow different clinical courses. The higher prevalence of internalizing disorders in females, compared to externalizing disorders such as ADHD[30], also supports the consideration of sex distribution when examining migraine and associated psychiatric comorbidities.

A review of the literature revealed that although there are a limited number of studies examining digital addiction and problematic gaming behaviors in the context of long-term pain and coping strategies, some important insights have been reported regarding this relationship. In particular, due to the psychosocial impact of chronic illnesses, children are at increased risk of developing comorbid psychiatric conditions such as social isolation and anxiety, which in turn may trigger problematic gaming behaviours through digital platforms[31]. Moreover, increased screen time and psychosocial difficulties can also act as triggers for headaches[32]. This situation may adversely affect the quality of life in individuals with migraine. In the current study, problematic online gaming behaviours were observed to be more prevalent in the children with migraine compared to the control group. While increased dopaminergic sensitivity is known to play a role in the pathophysiology of migraine[33], there is also evidence in the literature suggesting that excessive activation of the mesolimbic dopamine pathway contributes to addictive behaviours in IGD[34]. Although the data regarding the association between these two conditions are noteworthy, no studies to date have directly investigated this relationship. Further neuroimaging studies are needed in this field.

There is evidence suggesting that in children with migraine, total sleep duration may be normal or even prolonged in some cases, although sleep quality is often poor and fragmented[35]. Studies have proposed that this phenomenon may be related to increased trigeminal autonomic activity, dysfunction in melatonin rhythmicity, and imbalances within neurotransmitter systems involved in central pain modulation[36]. Another study reported that a reduction in REM sleep in patients diagnosed with migraine negatively affects sleep quality[37]. In addition, psychiatric comorbidities in the groups should be considered as potential factors affecting sleep quality. Even if the overall sleep duration appears normal, the restorative and recuperative effects of sleep are diminished, thereby exacerbating daytime functional impairment. Daytime dysfunction negatively affects social, cognitive, and academic functioning, ultimately reducing quality of life[35]. While the findings of the current study are consistent with the literature, they also indicate that sleep duration and sleep quality may be considered independent variables in the etiopathogenesis and clinical manifestations of migraine, and that this interaction may be bidirectional.

Study Limitations

There were some limitations to this study, which must be considered, primarily the cross-sectional design, the collection of data through self-report questionnaires, and the potential influence of individual differences and environmental factors on variables such as problematic internet use and sleep quality. In addition, the sample size and the fact that data were collected from a single centre restrict the generalizability of the study results. Further research with larger samples is warranted.

CONCLUSION

Migraine in children and adolescents is a complex, multifactorial disorder, arising from the interaction of genetic predisposition, environmental triggers, lifestyle deficiencies, and psychosocial stressors. A multidisciplinary evaluation of diagnosed children is crucial for the prevention of both behavioral problems and deteriorations in quality of life, and ito be able to influence the overall prognosis of the disorder.

Ethics

Ethics Committee Approval: Approval for this study was granted by the Non-Interventional Research Ethics Committee of the University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital (approval number: 2025/05-16, dated: 12.06.2025).

Informed Consent: Written and verbal informed consent was obtained from the participating children and their parents.

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Footnotes

Author Contributions

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

Conflict of Interest: The authors have no conflict of interest to declare.

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Original Article

An Analysis of Emergency Dental Care for Primary and Permanent Teeth in Pediatric Population

Pediyatrik Popülasyonda Süt ve Daimi Dişler için Acil Diş Bakımının Analizi

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ABSTRACT

Objective: Teeth that priorly and urgently require emergency dental care (SOS teeth) are evaluated through clinical and radiographic exams and primarily treated with root canal therapy and/or extraction in pediatric patients. It is important both to determine the prevalence and distribution of SOS teeth in children with primary and permanent dentition and to develop an appropriate treatment plan. This study assesses the prevalence of SOS teeth among the pediatric population based on gender, as well as types of teeth and their locations in the jaw.

Method: A total of 1391 patients without systemic diseases at the end of primary (ages 5-6; n=215) and the beginning of permanent dentition (ages 11-12; n=169) who visited the Pediatric Dentistry Clinic of Dokuz Eylül University, between November 1, 2022, and April 30, 2023, were included in the study. To identify SOS teeth, the Caries Assessment Spectrum and Treatment code 6 were used.

Results: SOS teeth were found in 62.3% of 5-6, and 19.5% of 11-12 year- old children. While no statistically significant difference was observed between gender and the presence of SOS teeth in terms of primary teeth, a significant difference was found regarding permanent teeth ($p<0.017$). SOS teeth appeared statistically significantly more often in the mandible than in the maxilla in terms of both primary and permanent molar teeth, ($p=0.003$, $p=0.001$, respectively).

Conclusion: SOS teeth were detected at a high rate in permanent and primary molar teeth. Therefore, the detection of SOS teeth and treatment planning should be included in the agenda of dentists.

Keywords: Emergency dental care, primary teeth, permanent teeth, pediatric population

ÖZ

Amaç: Acil diş bakımı (SOS dişleri), klinik ve radyografik olarak değerlendirilerek, çocuk hastalarda öncelikli olarak kök kanal tedavisi ve/veya çekim ile tedavi edilmesi düşünülen dişlerdir. Çocuklarda süt ve daimi dentisyon döneminde SOS dişlerinin yaygınlığını ve dağılımını belirlemek ve buna göre bir tedavi planı oluşturmak önemlidir. Bu çalışmada, çocuklarda SOS dişlerinin yaygınlığı cinsiyete, dişlere ve çenelerdeki lokalizasyonlarına göre değerlendirildi.

Yöntem: Dokuz Eylül Üniversitesi Çocuk Diş Hekimliği Kliniğine 1 Kasım 2022-30 Nisan 2023 tarihleri arasında başvuran, süt dişlenme döneminin sonunda (5-6 yaş) ve daimi dişlenme döneminin başında (11-12 yaş) olan ve sistemik hastalığı olmayan çocuklar çalışmaya dahil edildi. Bu dönemde kliniğimize gelen 1391 hastanın 215'i 5-6 yaşında, 169'u ise 11-12 yaşındaydı. SOS dişlerini tespit etmek için Çürük Değerlendirme Spektrumu ve Tedavi 6 kodu kullanıldı.

Bulgular: Beş ila altı yaş grubunda %62,3 oranında ve 11-12 yaş grubunda %19,5 oranında SOS dişleri tespit edildi. Cinsiyet ve süt dişlerinde SOS dişlerinin varlığı arasında istatistiksel olarak anlamlı bir fark bulunmazken, daimi dişlerde cinsiyetle SOS dişlerinin varlığı arasında fark tespit edildi ($p<0.017$). Süt ve daimi azı dişlerinde SOS dişleri maksilladan daha fazla mandibulada görüldü ve fark istatistiksel olarak anlamlıydı (sırasıyla $p<0.003$, $p<0.001$).

Sonuç: Daimi ve süt azı dişlerinde SOS dişleri yüksek oranda tespit edildi. Bu nedenle SOS dişlerinin tespiti ve tedavi planlaması diş hekiminin tedavi planlamasında önemli bir yer almalıdır.

Anahtar kelimeler: Acil bakım gerektiren dişler, süt dişleri, daimi dişler, çocuk

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INTRODUCTION

Dental caries in both primary and permanent teeth is a rising public health issue, except a few countries[1-4]. Early childhood caries, prevalent in primary teeth, can also affect permanent dentition[2]. While treating initial caries lesions in primary and permanent teeth is relatively simple, the planning, cost, and duration of treating deep dental caries involving the pulp are quite complex and lengthy[1-4].

Deep dental caries involving the pulp in primary teeth negatively impacts the child's nutrition, development, and jaw structure[1,2]. Similarly, deep dental caries affecting the pulp of a permanent teeth at an early age leads to short-, medium-, and long-term problems with occlusion, chewing, and bone development, as well as economic and social difficulties[1].

For many years, the most commonly used index for the detection of dental caries has been the decayed, missing, filled teeth (DMF-T) index, which represents the total number of decayed, missing, and filled teeth[5,6]. However, the DMF-T index does not provide sufficient information about clinical outcomes of dental caries, such as pulp involvement and tooth abscess[7].

To identify the stage of dental caries, the Caries Assessment Spectrum and Treatment (CAST) index is utilized (Table 1)[7]. The CAST index covers all stages of caries, from sound tooth surface to enamel and dentin caries lesions, pulp and periapical inflammation, and tooth loss due to caries[7].

This index can be applied during oral examinations to prioritize a patient's dental treatment needs and enable oral health authorities to evaluate emergency dental care. Teeth classified under CAST 6 code which identifies deep dental cavitation and pulp involvement require urgent treatment and, are considered priority teeth for treatment[8]. In recent years, teeth considered a priority for treatment and/or requiring urgent care in the literature have been defined as SOS teeth[8,9]. Unlike the CAST Index, "SOS teeth" are assessed clinically and radiographically to identify teeth that may need root canal treatment or extraction. The difference between diagnoses made based on CAST indexes, and presence of SOS teeth is revealed thorough evaluation of teeth during an oral exam, where teeth are dried with air and examined alongside clinical and radiographic findings[8-10].

Management of such teeth is expected to produce favorable outcomes in children, including better sleep patterns, balanced nutrition, improved academic performance, and an overall higher quality of life[1]. Additionally, identifying SOS teeth during oral exams enables dentists and oral health authorities to evaluate and plan emergency dental interventions accurately. Despite the availability of abundant data on the global epidemiology of dental caries in permanent teeth of children aged 12 years in recent years, there is limited information on the prevalence of deep caries involving the pulp[11,12]. The presence of deep caries involving the pulp in children in the primary dentition prompts the European Academy of Paediatric Dentistry to develop guidelines for managing deep caries in primary teeth in pediatric dentistry[13].

Table 1. Description of CAST codes[10]

CAST Code	Characteristic	Description	Tooth
0	Sound	No visible evidence of a distinct carious lesion is present	Healthy
1	Sealant	Pits and/or fissures are at least partially covered with a sealant material	
2	Restoration	A cavity is restored with an (in) direct restorative material	
3	Enamel	Distinct visual change in enamel only. A clear caries-related discolouration is visible, with or without localised enamel breakdown	Reversible
4	Dentine	Internal caries-related discolouration in dentine. The discoloured dentine is visible through enamel which may or may not exhibit a visible localised breakdown of enamel	Irreversible
5	Dentine	Distinct cavitation into dentine. The pulp chamber is intact	
6	Pulp	Involvement of the pulp chamber. Distinct cavitation reaching the pulp chamber or only root fragments are present	Serious morbidity
7	Abscess/Fistula	A pus-containing swelling or a pus-releasing sinus tract related to a tooth with pulpal involvement	Devital
8	Lost	The tooth has been removed because of dental caries	

This study aims to investigate the presence of SOS teeth in patients in the final stages of primary dentition (5-6 years old) and mixed dentition (11-12 years old) and to assess their distribution and prevalence based on gender of the patients, types of teeth involved, and affected jaws.

MATERIALS and METHODS

Participants and Study Design

Between November 1, 2022, and April 30, 2023, individuals who presented for dental examinations and reported other oral complaints were recruited from the Pediatric Dentistry Clinic of Dokuz Eylül. The study was approved by the Dokuz Eylül University Research Ethics Committee with protocol number 2023/19-21, date: 07.06.2023. Patients aged 5-6 and 11-12 years, without any systemic or genetic disorders, were specifically chosen for inclusion in the study. SOS teeth in the primary dentition of 5-6-year-old and in the permanent dentition of 11-12-year-old patients were assessed. An assent form and an informed consent form were signed by the children and their parents, respectively.

During this period, a total of 1391 patients visited our clinic. Of these, 215 out of 220 patients in the 5-6 age group (97.7%) and 169 out of 172 patients in the 11-12 age group (98.3%) agreed to participate in the study. Five patients were excluded from the study due to artifacts on their panoramic films. Following clinical examinations and a review of panoramic radiographic images, the presence of SOS teeth was determined. Individual forms were prepared for each patient, including age, gender, and CAST classification. Patients and their parents were informed about the study, and their signed informed consent forms were obtained.

Oral and Radiographic Examinations

A total of 384 patients, aged 5-6 and 11-12 years, who presented for dental treatment, underwent thorough clinical examinations at our clinic. After drying their primary and permanent teeth with air spray, examinations were conducted using mirrors and probes. The presence of SOS teeth in both primary and permanent dentitions was confirmed using the CAST classification (code 6), and detailed observations were meticulously documented on patient forms (Table 1). Panoramic radiographic images were carefully reviewed to support clinical assessments, and all findings were recorded correctly on patient forms. Notably, the evaluation of SOS teeth in children was carried out by a specialized pediatric dentist (G.K.). To avoid bias and variability in the interobserver evaluation, the radiographs were evaluated by a single dentist.

Inclusion and Exclusion Criteria

The study included children without systemic diseases aged 5-6, and 11-12 years, representing the primary, and late mixed dentition phases, respectively.

Statistical Analysis

Data analysis was performed using SPSS 24.00 software (IBM, Chicago, IL, USA). Stages of dental caries in all primary and permanent teeth were evaluated separately. Numerical variables were presented as means and standard deviations, while categorical variables as frequencies and percentages. Categorical data of groups were compared using Pearson's chi-square and Fisher's exact tests. The level of statistical significance was set at $p<0.05$.

RESULTS

SOS teeth were found in 62.3% of 215 patients aged 5-6 years, and while in 19.5% of 169 patients aged 11-12 years. Among a total of 4300 primary teeth evaluated in the 5-6 age group, SOS teeth were recorded in 385 teeth (8.9%). In the group of patients with permanent dentition, SOS teeth were not found in incisors; however, SOS teeth were present in 44 teeth (6.5%) of the 676 permanent first molars (PFMs) examined, along with two premolars.

When assessing the relationship between gender and the presence of SOS teeth, SOS teeth were more frequently detected in women than in men across both age groups. While there was no statistically significant difference in the presence of SOS teeth in the 5-6 age group ($p<0.658$), in the 11-12 age group, greater number of SOS teeth were found in males than in females ($p<0.017$) (Table 2). Regarding the distribution of SOS teeth in the 5-6 age group, higher number of SOS teeth were noted in the upper jaw deciduous incisors than in the lower jaw incisors. However, there were statistically significantly greater number of SOS teeth in the lower jaw deciduous molars than in the upper jaw molars ($p<0.001$).

In children aged 11-12 years, SOS teeth were found in two mandibular premolars; no SOS teeth were observed in the incisors. However, a statistically significantly higher prevalence of SOS teeth was observed in mandibular first permanent molars compared to their maxillary counterparts ($p<0.001$) (Table 3). In the 5-6 age group, SOS teeth were most frequently detected in mandibular primary first molars (29.3%), followed by mandibular primary second molars (27.4%), maxillary primary first molars (20.3%), maxillary primary second molars (7.9%), maxillary primary incisors (2.0%), and mandibular primary incisors (0.3%). The most frequently affected SOS teeth were found in both maxillary and mandibular first molars (Table 4).

The incidence of SOS teeth in maxillary first primary molars was found to be statistically significantly higher relative to the maxillary second primary molars (p<0.001); however, its incidence did not differ significantly in terms of mandibular primary molars (p<0.366). SOS teeth were more common in first and second molars in both maxillary and mandibular arches (p<0.001). When assessing primary molars of the right and left sides of the jaws, it was discerned that the prevalence of SOS teeth was greater on the left side (p<0.003).

Table 2. Distribution of SOS teeth in primary and permanent dentitions according to gender

Children in need of emergency dental care			SOS n (%)	Absent n (%)	p
Gender	Primary teeth	Female	62 (28.8)	40 (18.6)	0.658
		Male	72 (33.5)	41 (19.1)	
		Total	134 (62.3)	81 (37.7)	
	Permanent teeth	Female	8 (4.7)	64 (37.9)	0.017*
		Male	25(14.8)	72 (42.6)	
		Total	33 (19.5)	136 (80.5)	

Pearson's chi-square test (p<0.05)*

Table 3. Distribution of SOS teeth in primary and permanent dentitions

Affected teeth		SOS n (%)	Absent n (%)	p
Primary incisors	Maxillary	5 (2.3)	210 (97.7)	----
	Mandibular	2 (0.9)	213 (99.1)	
Primary molars	Maxillary	87 (40.5)	128 (59.5)	0.001*
	Mandibular	129 (60.0)	86 (40.0)	
Permanent incisors	Maxillary	-	169 (100.0)	----
	Mandibular	-	169 (100.0)	
Permanent Premolars	Maxillary	-	169 (100.0)	-----
	Mandibular	2 (1.2)	167 (98.8)	
Permanent molars	Maxillary	7 (4.1)	162 (95.9)	0.001**
	Mandibular	30 (17.8)	139 (82.2)	

Pearson's chi-square test (p<0.05)*, Fisher's exact test (p<0.05)**

Table 4. Distribution of SOS teeth in primary dentitions

Primary teeth requiring emergency dental care		SOS n (%)	Absent n (%)	p
Maxillary first and second primary molars	First primary molars (54-64)	87 (20.3)	343 (79.7)	0.001*
	Second primary molars (55-65)	34 (7.9)	396 (92.1)	
Mandibular first and second primary molars	First primary molars (74-84)	126 (29.3)	304 (70.7)	0.366
	Second primary molars (75-85)	118 (27.4)	312 (72.6)	
Maxillary primary molars	Right-left molars (54-55-64-65)	121 (14.1)	739 (85.9)	0.001*
Mandibular primary molars	Right-left molars (74-75-84-85)	244 (28.4)	616 (71.6)	
Maxillary-mandibular right molar	Right primary molars (54-55-84-85)	158 (18.4)	702 (81.6)	0.003*
Maxillary-mandibular left molars	Left primary molars (64-65-74-75)	208 (24.2)	652 (75.8)	
Maxillary primary incisors	Right-left incisors (51-52-53-61-62-63)	17 (2.0)	843 (98.0)	-------
Mandibular primary incisors	Right-left incisors (71-72-73-81-82-83)	3 (0.3)	857 (99.7)	

Pearson's chi-square test (p<0.05)*

In children aged 11-12 years, the presence of SOS permanent teeth was most commonly observed in the mandibular right PFMs (23 teeth), followed by the mandibular left PFMs (13 teeth), maxillary left PFMs (5 teeth), and maxillary right PFMs (3 teeth). Within this age range, SOS teeth were identified in two premolar teeth in the mandible, while they were not observed in permanent incisors (Table 5).

SOS teeth were statistically significantly more often found in mandibular FPMs rather than in maxillary FPMs (p<0.001). Similar to the primary molar teeth of children aged 5-6 years, SOS teeth were more frequently observed on the left side of the jaws than on the right side in the 11-12 age group, but without any statistically significant difference between incidence rates (p<0.061).

DISCUSSION

This study is a cross-sectional research trial aiming to determine the prevalence of SOS teeth in children aged 5-6 years with primary, and 11-12 years with permanent dentition to provide insights into this issue. We also used CAST index codes 6 and 7 to detect the presence of SOS teeth. However, there are many studies in the literature on the dental treatment of deep caries (codes 4-6) seen in primary and permanent teeth[13-16]. There are limited studies on the prevalence of urgent treatment (code 6) in primary and permanent teeth[14-18]. There are no studies in the literature on the prevalence of SOS teeth in primary and permanent teeth in the Turkish pediatric population.

Especially in developing countries, children often have SOS teeth at an early age due to inadequate, and bad oral hygiene habits. SOS teeth appear in primary and permanent dentition at an early stage and require urgent treatment, such as amputation or root canal therapy.

In this study the SOS teeth was found in 62.3% of patients with primary and in 19.5% of those with permanent dentition, indicating the need for endodontic treatment and/or extraction of one or more teeth. Generally, pulp involvement in both primary and permanent teeth is often accompanied by pain attacks, which negatively affect the child's quality of life[1,14]. Dental and developmental problems in children who experience premature loss of both primary and permanent teeth can affect their later years, leading to an increased need for complex and costly dental treatments[1].

In our study, while a significant difference was observed between gender and SOS teeth in terms of permanent dentition, no significant difference was observed for primary dentition. Some researchers have reported lack of any correlation between gender and the number of carious lesions in primary and permanent dentitions[14-17]; while others have reported significant correlations[1,18]. Almoznino et al.[8] showed that the number of SOS teeth in permanent dentition is higher in men than in women. This finding suggests that the lower prevalence of SOS teeth among girls could be due to their earlier onset of puberty and a generally higher emphasis on personal hygiene and self-care practices.

Table 5. Distribution of SOS teeth in permanent dentition

Permanent teeth requiring emergency dental care			SOS n (%)	Absent n (%)	p
First permanent molars (FPMs)	Maxillary	Right FPM (16)	3 (1.8)	166 (98.2)	---
		Left FPM (26)	5 (3.0)	164 (97.0)	
	Mandibular	Right FPM (36)	23 (13.6)	146 (86.4)	0.077
		Left FPM (46)	13 (7.6)	156 (92.4)	
	Maxillary	Right-left FPM (16-26)	8 (2.4)	330 (97.6)	0.001**
	Mandibular	Right-left FPM (36-46)	36 (9.8)	302 (89.2)	
	Right FPMs	Maxillary-mandibular (16-46)	16 (4.7)	322 (95.3)	0.061
	Left FPMs	Maxillary-mandibular (26-36)	28 (8.3)	310 (91.7)	
Permanent premolars	Maxillary premolars	Right-left (14-15-24-25)	-------	676 (100)	
	Mandibular premolars	Right-left (34-35-44-45)	2 (0.3)	674 (99.7)	----
Permanent incisors	Maxillary incisors	Right-left (11-12-13-21-22-23)	-	676 (100)	-------
	Mandibular incisors	Right-left (31-32-33-41-42-43)	-	676 (100)	
Pearson's chi square test *(p<0.05), Fisher's exact test (p<0.05)**					

Babaei et al.[14] evaluated the dental status of 739 primary school children aged 6-7 years according to the CAST index. In their study, they found that the indicated percentages of primary school children had dental caries CAST code 6 in their maxillary primary first molars (14.3%), maxillary primary second molars (17.9%), mandibular primary first molars (20.9%), and mandibular primary second molars (16.7%). Doneria et al.[19] evaluated the dental care status of 7-8-year-old children in India, and found CAST index code 6 dental caries in maxillary primary first molars in 29.0%, maxillary primary second molars in15.1%, mandibular primary first molar in 23.3%,and mandibular primary second molar in 23.3% of their study participants. In line with the results obtained by the researchers mentioned above and by us, the maxillary primary second molars were the least affected teeth. In both studies the incidence rates of CAST code 6 caries were slightly lower than ours, which we attributed to the higher number of children visiting our dental clinic due to dental problems.

In our study, the rate of SOS teeth (CAST index code-6) in permanent teeth was 19.5%. Que et al.[20] reported the first permanent molar CAST index code 6 in 16.9% of their pediatric patients aged 11-14 years. In our research, the incidence rates of SOS in permanent maxillary right and left first molars (1.8% vs 3.0 %), permanent mandibular left, and right first molars (13.6% vs 7.9%) were as indicated. Gudipaneni et al.[21] identified dental caries (CAST index code-6) in permanent first molars of children aged 7-9 in the maxillary right, and left first molars (5.9% vs 3.1%), in the mandibular left, and right first molars (9.0% vs 8.5%). Although the children's age range in their study was younger than ours, the rate of SOS teeth was quite similar. In our study, the prevalence of SOS teeth was 9.9% in mandibular FPMs,

compared to 2.4% in the maxillary FPMs. Among children in this age group, no SOS teeth were found in permanent incisors, but two mandibular premolar teeth required emergency dental treatment.

Similar to our study, in their study of 11-12-year-old children, Oter et al.[17] reported that maxillary FPMs require more intensive treatment than mandibular FPMs. Consistently, existing literature suggests a higher susceptibility of mandibular first permanent molars to decay compared to their maxillary counterparts[17-19].

In our study, although there was no statistically significant difference between permanent molar teeth of both sides of the upper and lower jaws in terms of the presence of SOS teeth ($p<0.061$), SOS teeth were more commonly observed in both primary molars ($p<0.003$) and permanent molar teeth on the left side rather than the right side. While most studies report no difference in the number of decayed and extracted teeth between the right and left sides of the jaws[21-23], Oter et al.[17] have reported a higher incidence of deep dentin caries and apical lesions on the left side of the jaws.

The study group showed a high occurrence of caries-prone primary molars and decayed, missing, or filled primary teeth, highlighting the critical importance of pulpal intervention as the main treatment for these dental problems. Since primary teeth play a crucial functional role in children's dental health and greatly influence the health of permanent teeth later on, the study emphasizes the need to focus on preventive care at an early stage in both primary and permanent dentitions.

We believe that applying preventive treatments such as fluoride and fissure sealants to primary and permanent teeth starting from an early age, while emphasizing timely prophylactic intervention may help prevent the formation of SOS teeth.

In our opinion, conduction of larger, multicenter, population-based studies is necessary to determine the prevalence of SOS teeth in primary and permanent dentitions.

Study Limitation

The limitation of the study is that it is a single-center study conducted on a small number of patients who applied to our clinic.

Conclusion

In summary, this study revealed the presence of SOS teeth in the primary teeth of children aged 5-6 years and in the permanent teeth of those aged 11-12 years. SOS teeth were more prevalent in males in the 11-12 age group. They were also quite common in especially mandibular primary molars and permanent first molars. These data have highlighted the importance of preserving primary molars and permanent first molars, especially in the early period, as well as the need for root canal treatment. Further research with a large population is needed to raise awareness on this critically important issue.

Ethics

Ethics Committee Approval: The study was approved by the Dokuz Eylül University Research Ethics Committee with protocol number 2023/19-21, date: 07.06.2023.

Informed Consent: An assent form and an informed consent form were signed by the children and their parents, respectively.

Footnotes

Author Contributions

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

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Original Article

Outpatient Parenteral Antimicrobial Therapy in Pediatric Patients

Pediatrik Hastalarda Ayaktan Parenteral Antimikrobiyal Tedavi

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ABSTRACT

Objective: Outpatient parenteral antimicrobial therapy (OPAT) has been developed as an alternative approach to hospital stay for the effective treatment of infections requiring long-term therapy. The aim of this study is to evaluate the clinical outcomes and hospital readmission rates of pediatric patients receiving OPAT.

Method: Pediatric patients aged between 1 month and 18 years who received antimicrobial treatment under the OPAT program were included in this retrospective study. The duration of OPAT, the antimicrobial treatments used, bed-days saved by OPAT, OPAT-related complications, and readmission rates were examined.

Results: A total of 21 patients were included in the study, and the median age of these patients was 85 months. The most common diagnosis was leishmaniasis, observed in 33.3% of cases. OPAT shortened hospital stays for a median of 6 days (interquartile range: 2-12.5) per case. However, 14.3% (n=3) of the patients required readmissions to the hospital. No infusion-related side effects were observed in any patients receiving OPAT.

Conclusion: Our data suggest that OPAT could be a good option for selected pediatric patients. However, further research and increased awareness are needed to promote the widespread use of OPAT for pediatric patients.

Keywords: Antibiotic, hospitalization, OPAT, pediatric

ÖZ

Amaç: Ayaktan parenteral antimikrobiyal tedavi (APAT), uzun süreli tedavi gerektiren enfeksiyonların etkili tedavisinde hastaneye yatışa alternatif bir yaklaşım olarak geliştirilmiştir. Bu çalışmanın amacı, APAT programı kapsamında antimikrobiyal tedavi alan pediatrik hastalarda klinik sonuçları ve hastaneye yeniden yatış oranlarını değerlendirmektir.

Yöntem: Bu retrospektif çalışmaya, APAT programı kapsamında antimikrobiyal tedavi alan 1 ay-18 yaş arasındaki pediatrik hastalar dahil edilmiştir. Çalışmada APAT süresi, kullanılan antimikrobiyal tedaviler, APAT ile önlenen hastaneye yatış günleri, APAT'a bağlı komplikasyonlar ve yeniden yatış oranları incelenmiştir.

Bulgular: Çalışmaya toplam 21 hasta dahil edilmiştir ve bu hastaların ortanca yaşı 85 aydır. Hastalarda en sık tanı %33,3 oranı ile leishmaniasis olarak saptanmıştır. APAT, olgu başına ortanca 6 gün (IQR: 2-12,5) hastaneye yatışı önlemiştir. Bununla birlikte, hastaların %14,3'ü (n=3) hastaneye yeniden yatış gerektirmiştir. APAT uygulanan hiçbir hastada infüzyona bağlı yan etki gözlenmemiştir.

Sonuç: Bulgularımız, APAT'ın seçilmiş pediatrik hastalar için iyi bir seçenek olabileceğini göstermektedir. Bununla birlikte, pediatrik APAT'ın yaygın kullanımını teşvik etmek için daha fazla araştırmaya ve farkındalığın artırılmasına ihtiyaç vardır.

Anahtar kelimeler: Antibiyotik, hastaneye yatış, APAT, pediatrik

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INTRODUCTION

Outpatient parenteral antimicrobial therapy (OPAT) was first described in 1974 for the treatment of children with cystic fibrosis and has since been adopted as an alternative approach to hospitalization for the effective treatment of infections requiring long-term therapy[1]. The benefits of OPAT include short-term absenteeism from school, reduced risk of healthcare-associated infections, cost-effective use of resources, and increased patient and parent satisfaction[2].

This treatment approach can be implemented in several ways: patients receive treatment in outpatient care units, patients or caregivers learn how to administer intravenous antimicrobial therapy and carry out the treatment at home, or nurses visit patients' homes to administer the treatment[3].

Like other medical practices, OPAT has potential risks as well as proven benefits. While comprehensive studies exist regarding the use of OPAT in adult patients, data on the use of OPAT for pediatric patients (p-OPAT) remain limited[1,4-6]. Due to pharmacokinetic differences, challenges in vascular access, and other age-related risk factors, pediatric patients should be evaluated separately from adults[6]. These factors highlight the need for further research on pediatric OPAT.

In this study, we aimed to evaluate pediatric patients who received OPAT over a five-year period in a tertiary care hospital in Türkiye. Additionally, OPAT-related complications and hospital readmission rates were examined to assess the safety profile of this treatment approach.

MATERIALS and METHODS

This single-center descriptive study was conducted at an education and research hospital that serves as a referral center for pediatric patients in the Aegean region of Türkiye. Pediatric patients aged between 1 month and 18 years who received outpatient parenteral antimicrobial treatment under the p-OPAT program at University of Health Sciences Türkiye, İzmir Faculty of Medicine, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital between January 2020 and January 2025 were included in the study. The study was conducted following approval granted from the Local Research Ethics Committee of University of Health Sciences Türkiye, İzmir Faculty of Medicine, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital (decision no: 2024/18-09, date: 26.12.2024) and in accordance with the World Medical Association Declaration of Helsinki Medical Research Involving Human Participants. Written informed consent was obtained from the parents of all patients.

At our institution, the p-OPAT program is coordinated by the pediatric infectious diseases team in collaboration with the ward nursing staff. Clinically stable patients who did not require ongoing inpatient hospitalization, and needed short-term parenteral antimicrobial therapy that could not be safely or effectively administered via oral route were eligible candidates for p-OPAT program. In addition, patients without severe comorbid conditions and with reliable caregivers capable of ensuring daily hospital visits and treatment follow-up were considered suitable for p-OPAT. Parenteral antimicrobial therapies were administered via peripheral intravenous catheters in all patients. Intravenous access was evaluated by nursing staff prior to each administration for patency and signs of infiltration, phlebitis, and local infection (if any). The frequency of intravenous catheterization was determined based on its functionality and clinical indication.

Patients were clinically assessed before each p-OPAT administration and were regularly monitored for intravenous access-related and other potential complications. After termination of p-OPAT, patients were observed for at least 30-60 minutes, particularly for infusion-related adverse reactions. OPAT was discontinued upon completion of the planned course of antimicrobial treatment, after achievement of sufficient clinical improvement allowing transition to oral therapy, development of p-OPAT-related complications, or the emergence of a need for hospital admission due to clinical deterioration.

In this study, clinical improvement was defined as resolution or marked improvement of infection-related clinical signs and symptoms during or at the end of the p-OPAT course, with successful completion of the planned p-OPAT without the need for additional intravenous therapy or hospital admission. Insufficient clinical improvement was defined as failure to achieve the expected clinical response during p-OPAT, persistence or worsening of symptoms, requirement for modification of antimicrobial therapy, or the need for hospital admission due to clinical deterioration. The number of inpatient hospital days saved due to the implementation of p-OPAT were also calculated.

Data obtained from medical records included demographic characteristics, diagnoses, bacteriological culture results, duration of p-OPAT, antimicrobial therapies used, hospital days saved due to p-OPAT, p-OPAT-related complications, and readmission rates.

Statistical Analysis

Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Numerical and categorical variables were analyzed using descriptive statistical methods. Continuous variables were expressed as medians and interquartile ranges (IQR), while categorical variables as frequencies and percentages.

RESULTS

The study population of 21 cases consisted of 12 (57.1%) female, and 9 (41.9%) male pediatric patients with a median age of 85 months (IQR: 23-150.5 months).Two patients were infants, aged 6 and 11 months.

All patients included in the study received p-OPAT in the outpatient units of the hospital. The primary diagnoses of patients enrolled in the p-OPAT program were as follows: leishmaniasis [33.3% (n=7)], pneumonia [23.8% (n=5)], soft tissue abscesses [19.0% (n=4)], upper respiratory tract infections [14.3% (n=3)], osteomyelitis [4.8% (n=1)] and a urinary tract infection [4.8% (n=1)]. Methicillin-resistant *Staphylococcus aureus* (*MRSA*) was isolated in 14.3% (n=3) of patients, including two cases with soft tissue abscesses and one with osteomyelitis. The demographic and clinical characteristics of the patients are detailed in Table 1.

Two infants included in the study were diagnosed with *MRSA*-related soft tissue abscesses. Teicoplanin was administered intravenously via a peripheral venous

Table 1. Demographic and clinical characteristics of the patients

Characteristics	n	%
Age (months), median (IQR)	85.0 (23.0-150.5)	
Female gender	12	57.1
Underlying disease		
Autism	1	4.8
Type of infection		
Skin and soft tissue: abscess	4	19.0
Respiratory: pneumonia	5	23.8
: upper respiratory tract infection	3	14.3
Musculoskeletal: osteomyelitis	1	4.8
Urinary tract infection	1	4.8
Leishmaniasis: visceral leishmaniasis	6	28.6
: cutaneous leishmaniasis	1	4.8
Positive culture from a sterile site		
Methicillin-resistant *S. aureus*	3	14.3
Type of intravenous access		
Peripheral venous catheter	21	100.0
Duration p-OPAT (days), median (IQR), min-max	2 (1-5), 1-21	
Bed-days saved, median (IQR)	6 (2-12.5)	
Hospital readmission	3	14.3

IQR: Interquartile range, p-OPAT: pediatric outpatient parenteral antimicrobial therapy, *S. aureus*: *Staphylococcus aureus* catheter in both infants, with a p-OPAT duration of 2 days in the 6-month-old infant and for 1 day in the 11-month-old infant. Neither infant required hospital readmission during or after p-OPAT.

Three patients aged 23, 83, and 211 months categorized under upper respiratory tract infections had p-OPAT for a duration of 1-5 days received the diagnosis of acute otitis. OPAT was initiated due to a more severe clinical course and the unsuitability or insufficiency of oral antibiotic therapy. These patients received short-course intravenous ceftriaxone administered via peripheral venous catheters.

In most cases, p-OPAT was initiated after a period of inpatient treatment and clinical stabilization. The median number of 8 (IQR: 0-15 days) inpatient days have passed before initiation of p-OPAT. Six patients were not hospitalized prior to initiation of p-OPAT. Among these cases, only one patient completed the entire p-OPAT course exclusively.

The median duration of p-OPAT was 2 days (1-IQR: 1-5 days) ranging between minimum 1, and maximum 21 days. All patients received p-OPAT through a peripheral venous catheter. Antimicrobial therapies received by the patients were as follows: liposomal amphotericin B (L-AmB) [33.3% (n=7], ertapenem [14.3% (n=3)], ceftriaxone [28.6% (n=6)] teicoplanin [28.6% (n=6)], and combination of ceftriaxone and teicoplanin [4.8% (n=1)]. The distribution of antimicrobial treatments by diagnoses is presented in Figure 1.

Reduced hospital length of stay, duration of p-OPAT, and clinical improvement rates according to diagnosis are summarized in Table 2. Overall, clinical improvement was achieved in 85.7% (18/21)of patients, who completed the planned p-OPAT course without the need for hospital readmission. OPAT reduced hospital length of stay for a median of 6 days (IQR: 2-12.5) per case. However, 14.3% (n=3) of the patients required hospital readmissions. One of these patients, who was being treated with ceftriaxone

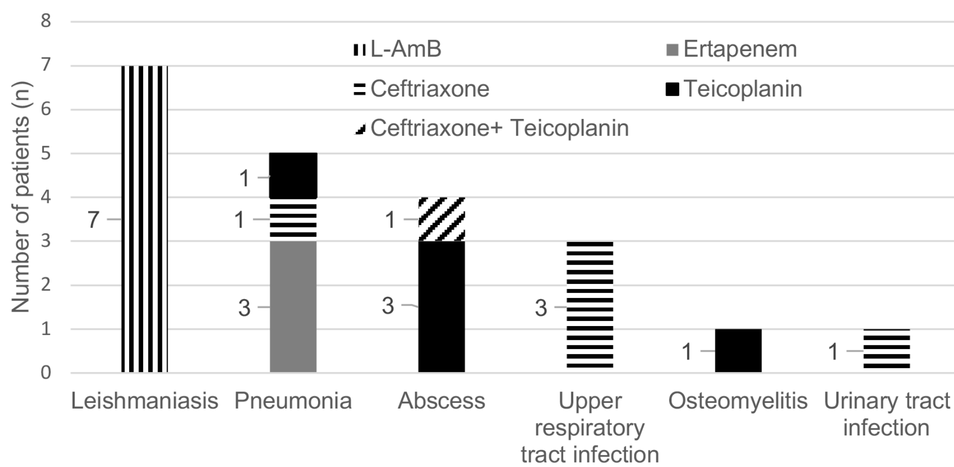

Figure 1. Distribution of antimicrobial therapies among patients with different infectious
L-AmB: liposomal amphotericin B

Table 2. outcomes of p-OPAT according to diagnoses

Diagnosis	n	Duration of p-OPAT (days), median (IQR)	Saved hospital days, median (IQR)	Clinical improvement, n (%)
Leishmaniasis	7	2 (1-2)	10 (7-15)	6/7 (85.7)
Pneumonia	5	5 (3-10)	5 (3-10)	5/5 (100.0)
Abscess	4	2 (1.3-14.0)	2 (1.3-14.0)	3/4 (75.0)
Upper respiratory tract infection	3	1 (1-1)	1 (1-1)	3/3 (100.0)
Osteomyelitis	1	21 (-)	21 (-)	1/1 (100.0)
Urinary tract infection	1	1 (-)	1 (-)	0/1 (0.0)

IQR: Interquartile range, p-OPAT: pediatric outpatient parenteral antimicrobial therapy and teicoplanin for a soft tissue abscess under the p-OPAT program, was hospitalized due to insufficient clinical improvement and the need for further monitoring on day 2 of p- OPAT. Another patient receiving L-AmB for the treatment of leishmaniasis developed elevated transaminase levels during follow-up, necessitating hospitalization for treatment and observation on day 1 of p-OPAT. Additionally, a patient treated with ceftriaxone under p-OPAT protocol for a urinary tract infection was rehospitalized due to abdominal pain and fever on day 1 of p-OPAT. No infusion-related adverse events were observed in any of the patients included in the p-OPAT program.

DISCUSSION

Our study focused on examining the clinical and microbiological characteristics of patients receiving p-OPAT, the antimicrobial therapies used, p-OPAT-related complications, and readmission rates in a children's hospital. Clinical improvement was observed in 85.7% of cases in our p-OPAT cohort, with no need for readmissions. The median duration of p-OPAT was 2 days, and the most commonly used antimicrobial therapy was L-AmB. In patients receiving antimicrobial treatment under the p-OPAT program, length of hospital stay was relatively reduced for a median of 6 inpatient days. Our youngest two patients, aged 6 and 11 months, completed p-OPAT without developing any complications.

The notably short median p-OPAT duration of 2 days observed in our cohort may reflect the predominant use of p-OPAT as a step-down strategy following inpatient treatment and clinical stabilization. Indeed, a considerable proportion of patients had varying lengths of hospitalization prior to initiation of p-OPAT. Guidelines of p-OPAT and pediatric good-practice recommendations emphasize that eligibility for p-OPAT should be decided based on a combined assessment of clinical stability, the absence of a requirement for continued inpatient care, the feasibility of using safe outpatient parenteral therapy, and the availability of reliable caregiver support and follow-up. Indeed, our patient selection criteria strictly adhered to these broadly recommended principles[7,8].

The most common diagnosis in our study was leishmaniasis, accounting for 33.3% (n=7) of cases, and these patients were treated with L-AmB. The most frequently used antimicrobial therapies for p-OPAT are antibiotics, while antifungal agents are rarely preferred[9]. The main reason for this preference is the presence of underlying comorbidities such as hematological diseases or immune deficiencies in these patients. In an OPAT study conducted in adults and published by Gil-Navarro et al.[2], although no significant difference was found between the effectiveness and safety of antifungal treatment and antibiotic use; it was observed that the rate of comorbidities was higher in patients receiving antifungal treatment. Therefore, certain criteria have been recommended for the safe and effective use of antifungal treatment for OPAT including microbiological confirmation of the diagnosis, control of the source of infection, administration of initial antifungal treatment in a hospital setting, ensuring the patient's hemodynamic stability, and regular follow-up by an infectious diseases specialist[2]. Studies evaluating p-OPAT for leishmaniasis are limited. However, a study reporting a saving of 14.2 bed-days per case emphasized that p-OPAT could be an effective alternative to hospitalization for leishmaniasis and other tropical diseases[10]. The recommended regimen for the treatment of leishmaniasis is the administration of 3 mg/kg L-AmB on days 1-5, 14, and 21, with a total dose of 21 mg/kg[11]. The patients in our cohort received their initial L-AmB treatment during hospitalization, and after their clinical condition stabilized, they were discharged. Three of these patients received p-OPAT on day 21, and four received p-OPAT on days 14 and 21. Only one patient in our study required readmission due to elevated transaminases, but discontinuation of the antimicrobial used was not required.

Ertapenem is an important option for the management of p-OPAT due to its once-daily dosing regimen for the treatment of intra-abdominal infections, complicated skin and soft tissue infections, community-acquired pneumonia, and complicated urinary tract infections[12]. Ertapenem is effective against both Gram-negative and Gram-positive bacteria, as well as anaerobic bacteria, due to its broad-spectrum activity; however, it is not effective against *Enterococcus species (Enterococcus spp.)*, *Pseudomonas aeruginosa*, or *Acinetobacter spp.* [13]. Although past experience is limited, previous studies have shown that patients with complicated urinary tract infections, intra-abdominal infections, and community-acquired pneumonia have been successfully treated using ertapenem in cases with p-OPAT[13-15]. In our cohort, ertapenem was successfully administered to three patients diagnosed with complicated community-acquired pneumonia, and no p-OPAT-related complications or readmissions were observed.

Staphylococci and *streptococci* are the most common causative agents of osteomyelitis, complicated skin and soft tissue infections, and endocarditis[16]. This group of diseases typically requires prolonged intravenous therapy lasting approximately six weeks. Teicoplanin is effective against *staphylococci* (including methicillin-resistant strains), *streptococci*, and *Enterococcus spp*[17]. In our study, teicoplanin was used within the p-OPAT program for the management of soft tissue abscesses, osteomyelitis, and pneumonia, while *MRSA* was identified in three of these patients. One of the patients receiving teicoplanin was also on combination therapy with ceftriaxone. This patient required readmission for monitoring purposes due to insufficient clinical improvement; however, no changes to the treatment regimen were necessary. The patients in our study received teicoplanin once daily. Although studies investigating the use of teicoplanin three times a week in osteomyelitis and soft tissue infections have shown successful outcomes, these findings need to be validated with new data[16,18].

Ceftriaxone is the most frequently prescribed antibiotic within the p-OPAT program[19]. Its primary indications include skin and soft tissue infections, bone and joint infections, and Lyme disease; however, it has been also successfully used in the treatment of other infectious diseases, such as pneumonia, upper respiratory tract infections, and urinary tract infections[19-21]. In our clinic, ceftriaxone was used within the p-OPAT program for upper respiratory tract infections, pneumonia, urinary tract infections, and soft tissue abscesses. One patient treated for a urinary tract infection required readmission to the hospital due to fever and abdominal pain during follow-up. None of the patients receiving ceftriaxone through p-OPAT protocol experienced infusion-related side effects.

In pediatric OPAT studies, adverse event rates of up to approximately 30% have been reported, with intravenous access–related problems being the most common complications[6]. In previous studies evaluating the safety of using central venous catheters during OPAT in children, complication rates ranged between 29% and 33%, whereas a study in which most patients were managed with peripheral cannulas reported an overall complication rate of 11%[3]. The absence of peripheral venous catheter–related complications in our study is noteworthy and may be explained by several factors: (i) the predominantly short duration of p-OPAT in our cohort, (ii) the use of peripheral venous access rather than central catheters, and (iii) routine nursing assessment of intravenous access prior to each administration and post-infusion observation. Nevertheless, although p-OPAT-related complications were routinely recorded during clinical follow-up, given the retrospective design of the study, it should be considered that minor events such as mild infiltration or irritation may not always have been reflected in the medical records. In contrast, 14.3% of the patients in our cohort required hospital readmission. Our readmission rates for various reasons have been reported to range between 11% and 17% in consistent with those previously reported[3,6].

Study Limitations

The study has several limitations. First of all, the diagnosis and indications, as well as the antimicrobial drugs used, showed a heterogeneous distribution, which might be a confounding factor. In addition, the sample size was relatively small. To our knowledge, data on use of OPAT in pediatric patients from Turkey are limited, and this study provides insights that may inform future research. The single-center and retrospective design of the study, along with the relatively small sample size, limited the generalizability of the results obtained.

CONCLUSION

In conclusion, our data suggest that p-OPAT may be a good choice for selected pediatric patients. Pediatric OPAT programs should be further investigated, expanded, and structural frameworks should be developed to promote wider implementation of OPAT in children.

Ethics

Ethics Committee Approval: The study was conducted following approval granted from the Local Research Ethics Committee of University of Health Sciences Türkiye, İzmir Faculty of Medicine, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital Hospital (decision no: 2024/18-09, date: 26.12.2024) and in accordance with the World Medical Association Declaration of Helsinki Medical Research Involving Human Participants.

Informed Consent: This is a retrospective study.

Footnotes

Author Contributions

Concept: H.Ö, D.E., P.K., N.B., Design: H.Ö, D.E., A.A.K., Data Collection or Processing: H.Ö, D.E., B.K.Ç., Ç.Ö., Analysis or Interpretation: H.Ö., A.Ö., G.G.Ö., A.A.K., D.O., N.B., İ.D., Literature Search: H.Ö, A.Ö., G.G.Ö., Ç.Ö., Writing: H.Ö, D.E., P.K., B.K.Ç., A.Ö., Ç.Ö., G.G.Ö., A.A.K., D.O., N.B., İ.D.

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Original Article

Mothers' Perceptions and Attitudes Toward Human Milk Banking Scale: A Scale Development Study

Annelerin Anne Sütü Bankacılığına İlişkin Algı ve Tutumlar Ölçeği: Bir Ölçek Geliştirme Çalışması

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ABSTRACT

Objective: The aim of this investigation is to construct and psychometrically evaluate a novel measurement instrument designed to capture maternal perceptions and attitudes regarding donor milk services.

Method: An instrument development investigation was undertaken among mothers between 18-49 years of age with their offspring under sixty months who presented to the pediatric department of Izmir Bakirçay University Çiğli Training and Research Hospital. Information about study participants was gathered using a demographic information form and the newly constructed "Perceptions and Attitudes Toward Human Milk Banking".

Results: Psychometric evaluation encompassed content validity assessment, dimension reduction through principal axis factoring, structural verification via latent variable modeling, and homogeneity assessment through estimation of coefficient alpha with item-scale correlation analysis. Upon completion of item refinement procedures, the finalized eighteen-item version exhibited superior homogeneity (coefficient alpha=0.925). Sampling adequacy assessment yielded a Kaiser-Meyer-Olkin coefficient of 0.789, while the Bartlett sphericity examination reached the level of statistical significance ($p<0.001$). Dimension reduction revealed a tripartite structure accounting for 70.089% of score variability including Communal Encouragement and Behavioral Inclination ($\alpha=0.943$), Informational and Security Consciousness ($\alpha=0.874$), and Personal Evaluations and Reservations ($\alpha=0.655$). Confirmatory factor analysis demonstrated satisfactory correspondence between the hypothesized model and observed data ($\chi^2/df=1.818$; Comparative Fit Index=0.965; Root Mean Square Error of Approximation=0.064). Time-dependent consistency assessment through repeated applications yielded intraclass correlation coefficients ranging from 0.91-0.93.

Conclusion: This scale constitutes a psychometrically sound 18 item-ratng instrument featuring three constituent domains appropriate for capturing mothers' perceptions and attitudes concerning donor milk services.

Keywords: Human milk banking, perception, validity, reliability, attitude

ÖZ

Amaç: Bu araştırmanın amacı, annelerin anne sütü bankacılığına ilişkin bakış açılarını ve tutumlarını değerlendirmek üzere tasarlanmış yeni bir ölçme aracını geliştirmek ve psikometrik özelliklerini incelemektir.

Yöntem: Bu ölçek geliştirme çalışması, İzmir Bakırçay Üniversitesi Çiğli Eğitim ve Araştırma Hastanesi Pediatri Servisi'ne başvuran, 18-49 yaş aralığında ve beş yaş altı çocuğa sahip anneler arasında yürütülmüştür. Katılımcı bilgileri, sosyodemografik bilgi formu ve yeni geliştirilen "Anne Sütü Bankacılığına Yönelik Algı ve Tutumlar Ölçeği" aracılığıyla toplanmıştır.

Bulgular: Psikometrik değerlendirme; kapsam geçerliği analizi, temel eksen faktörleştirme yoluyla boyut indirgeme, doğrulayıcı faktör analizi ile yapısal doğrulama ve Cronbach alfa katsayısı ile madde-toplam korelasyon analizi aracılığıyla iç tutarlılık değerlendirmesini kapsamıştır. Madde analizi süreçlerinin tamamlanmasının ardından, son hali verilen on sekiz maddelik versiyon üstün iç tutarlılık göstermiştir (Cronbach $\alpha=0.925$). Örneklem yeterliliği değerlendirmesi Kaiser-Meyer-Olkin katsayısını 0.789 olarak belirlemiş, Bartlett küresellik testi istatistiksel anlamlılığa ulaşmıştır ($p<0.001$). Açımlayıcı faktör analizi,

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toplam varyansın %70.089'unu açıklayan üç faktörlü bir yapı ortaya koymuştur: Sosyal Destek ve Davranışsal Niyet (α=0.943), Bilgi ve Güvenlik Farkındalığı (α=0.874) ve Bireysel Algılar ve Çekinceler (α=0.655). Doğrulayıcı faktör analizi, önerilen model ile gözlenen veriler arasında kabul edilebilir uyum göstermiştir (χ^2/df=1.818; CFI=0.965; RMSEA=0.064). Tekrarlanan uygulamalar yoluyla zamana bağlı tutarlılık değerlendirmesi, 0.909 ile 0.925 arasında değişen sınıf içi korelasyon katsayıları vermiştir.

Sonuç: Bu ölçek annelerin anne sütü bankacılığına ilişkin algı ve tutumlarını değerlendirmek için uygun, üç alt boyuttan oluşan, geçerli ve güvenilir 18 maddelik bir ölçme aracıdır.

Anahtar Kelimeler: Anne sütü bankacılığı, algı, geçerlik, güvenirlik, tutum

INTRODUCTION

Breast milk constitutes the primary nutritional source for newborns, furnishing unparalleled sustenance for pediatric maturation and advancement. International health authorities advocate for uninterrupted maternal feeding throughout the initial half-year of infants' life, with subsequent maintenance alongside supplementary nourishment extending to the second year of life[1]. Maternal milk fortifies immunological defenses of the infants, shields against pathogenic invasions, facilitates neurodevelopmental progression, and attenuates enduring susceptibilities to cardiovascular pathology, excessive adiposity, and metabolic dysregulation[2,3]. The advantages of maternal feeding transcend offspring wellness to incorporate benefits for maternal physiological outcomes.

Statistical documentations released by Turkish health registries for the year 2024 indicate that maintaining only breastfeeding during the initial half-year of life reached 40.7%, subsequently diminishing to 3% among infants between six and nine months of age[4]. Domestic investigations have documented heterogeneous nursing durations[5-7], suggesting that breastfeeding represents an enduring practice in Türkiye. Nevertheless, irrespective of its prevalence and persistence, universal accessibility to sufficient provision of breast milk remains unattainable for all newborns under all circumstances.

Under circumstances encompassing premature delivery, maternal pathology, postponed initiation of milk production, transient parent-offspring disconnection, or heightened neonatal nutritional demands, provision of supplementary breast milk may prove indispensable even when maternal breastfeeding continues[1]. Within such contexts, donor milk services materialize as a consequential practice that augments and supplements rather than directly superseding maternal breastfeeding. Global health organizations underscore the importance of nourishing infants incapable of receiving biological maternal milk with donated breast milk as opposed to commercial formulations[8].

Donor milk facilities undertake acquisition, evaluation, treatment, preservation, and allocation of maternal breast milk donated to neonates requiring supplementation[9]. Nonetheless the number of such international establishments continues to expand. Despite governmental inclusion of milk banking within the 2013-2017 strategic framework, no operational donor milk facility presently functions in Türkiye[1,2]. Theological and sociocultural apprehensions, notably considerations (ie.fatwas) concerning lactational kinship within Islamic jurisprudence, represent substantial impediments[2,8]. However, predominantly Muslim nations including Malaysia and Kuwait have successfully instituted culturally attuned operational frameworks[1,2,8].

For the implementation of donor milk services in Türkiye, thorough evaluation of communal perspectives and dispositions proves indispensable. Despite the necessity of assessing multifaceted constructs encompassing informational awareness, theological-cultural viewpoints, security apprehensions, communal encouragement, and service utilization willingness, no standardized Turkish measurement instrument currently exists. Consequently, this investigation sought to construct the Mothers' Perceptions and Attitudes Toward Human Milk Banking Scale (PAT-HMBS) and evaluate its measurement characteristics to facilitate policy formulation, public enlightenment, and clinical consultation.

MATERIAL and METHODS

Study Design

This investigation was undertaken both to construct the "Mothers' Perceptions and Attitudes Toward Human Milk Banking Scale" and to appraise its measurement characteristics.

Target Population and Participants

The target population encompassed mothers presenting to the pediatric department of İzmir Bakırçay University Çiğli Training and Research Hospital throughout the investigation timeframe. Selection of study participants was performed using accessibility-based sampling method among mothers satisfying eligibility requirements. Eligibility requirements encompassed: age range of 18-49 years, possession of minimum one offspring under sixty months of age, capacity to comprehend Turkish language, and consensual agreement to participate. Mothers providing incomplete or erroneous responses were not included in the study.

Methodological guidelines for instrument development investigations advocate inclusion of number of participants representing 5-10 multiples of statement counts or enrollment of minimum 300 individuals[10,11]. Authorities recommend enrollment of minimum 150 participants for dimension reduction procedures and 200 participants for structural verification analyses[12,13,14]. Correspondingly, for the preliminary twenty-four-item instrument, 200 participants were recruited for dimension reduction and 200 participants for structural verification, producing a cumulative sample of 400 mothers.

Assessment Instruments

Demographic Information Form

This questionnaire was formulated by the research team drawing upon pertinent scholarly literature[2,5-10]. The form encompassed 23 inquiries addressing attributes of the participants (age, conjugal condition, scholastic attainment, occupational engagement, vocational classification, subjective economic standing, geographical habitation), reproductive and offspring particulars (number of offspring under five years of age, age of the youngest offspring, parturition modality, gestational duration at the most recent delivery, history of premature birth, and neonatal intensive treatment, nursing status, duration of cumulative nursing, onset of supplementary nourishment), health and behavioral determinants (presence of a chronic pathology, routine use of pharmaceutical consumption, smoking status, body composition index), healthcare accessibility and assistance (routine medical examinations, lactation consultation, perceived communal assistance).

Mothers' Perceptions and Attitudes Toward Human Milk Banking Scale (PAT-HMBS)

This measurement instrument was formulated by the research team. Throughout construction of this instrument, exhaustive review of scholarly literature was initially undertaken to delineate dimensions encompassing informational awareness, consciousness, security perception, theological and sociocultural dispositions, communal orientations, and willingness to utilize service concerning donor milk banking. Drawing upon these dimensions, a repository of 24 items was generated. The instrument employs a five-category Likert response format, quantified as "Completely Disagree" (1), "Disagree" (2), "Uncertain" (3), "Agree" (4), and "Completely Agree" (5). No inversely-scored items exist within the instrument. The definitive instrument version comprises 18 items distributed across three constituent domains: Communal Encouragement and Behavioral Inclination (11 items; scoring span: 11-55), Informational and Security Consciousness (4 items; scoring span: 4-20), and Personal Evaluations and Reservations (3 items; scoring span: 3-15). Cumulative instrument scores ranges between 18 to 90 points, with higher scores signifying increasingly favorable perspectives and dispositions toward donor milk services.

Instrument Construction Procedures

Statement Repository Generation

During the preliminary instrument construction phase, exhaustive examination of domestic and international scholarly literature concerning donor milk banking was undertaken[2,3,8,9,15-19]. Investigations addressing informational comprehension, security apprehensions, theological and sociocultural perspectives, communal orientations, and willingness to utilize health care service were scrutinized. Five conceptual dimensions emerged, and statements representing each dimension were composed to establish a repository of 24 items.

Specialist Evaluation and Content Appropriateness

The repository of statements was submitted to 10 specialists possessing doctoral credentials in Maternal Health and Obstetric Nursing or Pediatric Nursing for the assessment of content appropriateness. The Davis methodology used guided evaluation procedures of specialists[20]. Specialists categorized each statement as "(a) suitable," "(b) requires minimal modification," "(c) requires substantial modification," or "(d) unsuitable." The Content Validity Index (CVI) for each statement was computed as the proportion of specialists selecting categories (a) or (b). CVI values ≥0.80 were deemed satisfactory[21,22]. Within this investigation, statement-level CVI values spanned 0.90 to 1.00, with instrument-level CVI reaching 0.94 percent.

Preliminary Testing

Subsequent to assessments by specialists, preliminary testing was undertaken with 10 mothers satisfying eligibility criteria to assess comprehensibility, implementability, statement lucidity, and time to complete the test. Direct interpersonal interviews were conducted, with participants requested to appraise the lucidity and ease of response for each statement. Ambiguous or potentially misinterpreted statements underwent revision based upon observations of participants which was completed in approximately 8-10 minutes To preclude potential familiarization effects, participants who performed preliminary testing were not included in the primary sample.

Information Gathering Procedure

The investigation was performed at the pediatric department of İzmir Bakırçay University Çiğli Training and Research Hospital spanning October 6, 2025, through January 2, 2026, subsequent to receiving ethical approval from the Amasya University Rectorate–Non-Interventional Clinical Research Ethics Committee (decision no.: 2025000172, date: 02.10.2025), and institutional clearance. Mothers presenting to ambulatory and inpatient units received information about the investigations, and written authorization was obtained from those satisfying eligibility requirements and consenting to participate. Information was gathered through direct interpersonal interviews conducted individually within a confidential consultation space at suitable times following verification of safety and welfare of offspring. Participants received information regarding investigation objectives, voluntary participation, and information confidentiality. Each questionnaire required approximately 10-15 minutes for completion.

Statistical Analysis

Analytical procedures were performed utilizing IBM SPSS Statistics 22.0 and IBM AMOS 24.0 statistical software programs. Descriptive computations were performed: categorical variables underwent summarization as frequencies and proportions, while continuous variables were expressed as arithmetic means, spread measures, and value ranges. Distribution characteristics were evaluated through asymmetry and peakedness indices.

Validity Examinations: Structural validity was evaluated through dimension reduction and structural verification procedures. Antecedent to dimension reduction, information appropriateness for factorization was appraised through the Kaiser-Meyer-Olkin (KMO) sampling adequacy coefficient and Bartlett sphericity examination. KMO values ≥0.60 and significant Bartlett sphericity examination outcomes ($p<0.05$) were deemed satisfactory[23]. Principal axis extraction with orthogonal rotation was employed for dimension reduction. Statements exhibiting dimension loadings ≥0.40 were preserved[22]. Structural verification was undertaken on an autonomous sample to corroborate the dimensional configuration. Model correspondence was appraised through application of chi-square test to degrees of freedom ratio (χ^2/df), Comparative Fit Index (CFI), Tucker-Lewis Index (TLI), Normed Fit Index, Goodness of Fit Index (GFI), Root Mean Square Error of Approximation (RMSEA), and Standardized Root Mean Square Residual.

Homogeneity Examinations

Homogeneity was assessed through Cronbach coefficient alpha; and values ≥0.70 were deemed satisfactory[23]. Adjusted statement-scale correlations were estimated and correlations ≥0.30 signified adequate statement discrimination[22]. Temporal consistency underwent evaluation through intraclass correlation coefficients (ICC) derived from relevant tests conducted at fourteen-day intervals.

Discriminative Capacity

To appraise the instrument's capacity for intergroup differentiation, independent sample comparisons were undertaken contrasting the lowest 27% and highest 27% subgroups based upon cumulative scores. The level of statistical significance was set at $p<0.05$ for all examinations.

RESULTS

The preponderance of participants (61.5%) fell within the 31-40 year age bracket, 89.5% of them were married, 32.5% of them were secondary school graduates, and 42% of them were not engaged in an employment external to the household. Approximately 46% of them indicated that their earnings approximated their expenditures. Among participants, 43% of them resided within provincial centers and 50% of them had two offspring. Concerning parturition modality, 52% of them had undergone surgical delivery, with approximately one-third possessing histories of premature birth and neonatal intensive treatment admission. Regarding nursing status, 55% had discontinued nursing while 35% were presently nursing. Mean chronological age of participants was 33.55±5.88 years, mean age of the youngest offspring was 16.02±13.99 months, mean cumulative duration of nursing was 8.62±5.76 months, and mean age for starting supplementary nourishment was 3.91±1.99 months (Table 1).

Table 1. Distribution of participants according to their descriptive characteristics

Variables	n	%
Age (years)		
≤≤30	50	25.0
31-40	123	61.5
≤41	27	13.5
Marital status		
Married	179	89.5
Single	21	10.5
Educational level		
Primary/secondary school	36	18.0
High school	65	32.5
Associate degree	44	22.0
Bachelor’s degree	44	22.0
Graduate degree	11	5.5
Employment status		
Full-time	70	35.0
Part-time	46	23.0
Unemployed/homemaker	84	42.0
Perceived income		
Income lower than expenses	83	41.5
Income equal to expenses	92	46.0
Income higher than expenses	25	12.5
Place of residence		
Provincial center	86	43.0
District	78	39.0
Town/village	36	18.0
Number of children under 5 years of age		
1	91	45.5
2	100	50.0
3	9	4.5
Delivery		
Vaginal	96	48.0
Cesarean section	104	52.0
History of preterm birth		
Yes	57	28.5
No	143	71.5
History of NICU admission		
Yes	57	28.5
No	143	71.5
Breastfeeding status		
Currently breastfeeding	70	35.0
Expressing milk	17	8.5

Table 1. Continued

Variables	n	%
Stopped breastfeeding	110	55.0
Never breastfed	3	1.5
Received breastfeeding counseling		
Yes	179	89.5
No	21	10.5
Continuous variables	**Mean +/- SD**	**Min-max**
Age (years)	33.55+/-5.88	22-44
Age of youngest child (months)	16.02+/-14.00	2-53
Gestational week at last delivery	37.61+/-2.27	32-43
Duration of total breastfeeding (months)	8.62+/-5.76	0-26
Age at starting nutrition with complementary food (months)	3.91+/-1.99	0-7
Body mass index (kg/m^2)	26.14+/-3.87	20.3-36.7

NICU: Neonatal Intensive Care Unit

Homogeneity and Statement Analysis

The preliminary twenty-four-item PAT-HMBS version exhibited a Cronbach coefficient alpha of 0.872, signifying satisfactory homogeneity and suggesting that statements generally assessed the identical construct. Scrutiny of adjusted statement-scale correlations disclosed that most statements surpassed the 0.30 satisfactory threshold. Nevertheless, several statements (PAT-HMBS6, PAT-HMBS8, PAT-HMBS10, PAT-HMBS15, PAT-HMBS20) exhibited minimal or inverse statement-scale correlations, signifying inadequate correspondence with the underlying construct. Moreover, elimination of these statements produced elevated Cronbach alpha values, substantiating the adverse influence of these problematic statements on homogeneity. Subsequent to elimination of statements exhibiting minimal or inverse statement-scale correlations, the definitive eighteen-statement version exhibited a Cronbach alpha of 0.925, signifying its superior homogeneity (Table 2).

Dimension Reduction Analysis

Dimension reduction analysis was undertaken to scrutinize structural validity of the instrument. Antecedent to analysis, appropriateness of the information concerning factorization was assessed. The KMO coefficient of 0.789 signified adequate sampling appropriateness. Bartlett sphericity examination achieved statistical significance (χ^2=3680.893; df=153; $p<0.001$), corroborating sufficient inter-variable correlations for factorization.

Table 2. Item analysis results				
Items	**Initial item-total correlation (r)**	**Initial Cronbach's α if item deleted**	**Final item-total correlation (r)**	**Final Cronbach's α if item deleted**
PAT-HMBS1	0.733	0.860	0.712	0.919
PAT-HMBS2	0.375	0.871	0.370	0.931
PAT-HMBS3	0.638	0.862	0.630	0.921
PAT-HMBS4	0.554	0.864	0.557	0.923
PAT-HMBS5	0.401	0.869	0.416	0.927
PAT-HMBS6	0.079	0.880	-	-
PAT-HMBS7	0.361	0.870	0.373	0.927
PAT-HMBS8	-0.172	0.883	-	-
PAT-HMBS9	0.530	0.865	0.525	0.923
PAT-HMBS10	-0.124	0.883	-	-
PAT-HMBS11	0.177	0.876	-	-
PAT-HMBS12	0.479	0.866	0.498	0.924
PAT-HMBS13	0.548	0.864	0.534	0.923
PAT-HMBS14	0.646	0.863	0.662	0.921
PAT-HMBS15	-0.089	0.885	-	-
PAT-HMBS16	0.800	0.856	0.794	0.917
PAT-HMBS17	0.822	0.858	0.827	0.917
PAT-HMBS18	0.779	0.858	0.772	0.918
PAT-HMBS19	0.794	0.859	0.785	0.918
PAT-HMBS20	0.057	0.878	-	-
PAT-HMBS21	0.761	0.859	0.789	0.918
PAT-HMBS22	0.779	0.859	0.799	0.918
PAT-HMBS23	0.704	0.861	0.739	0.919
PAT-HMBS24	0.713	0.860	0.732	0.919

Initial Cronbach alpha=0.872, Final Cronbach alpha=0.925, r=Item-total correlation

Principal axis extraction with orthogonal rotation generated a tripartite solution with characteristic values exceeding 1.0, which proved to be theoretically coherent. The three dimensions accounted for 70.089% of cumulative variance, surpassing the 60% threshold deemed satisfactory for behavioral sciences (Table 3).

Dimension 1 (Communal Encouragement and Behavioral Inclination) possessed a characteristic value of 8.925 and accounted for 35.797% of variance. Statements loading on this dimension addressed perspectives regarding breast milk contribution as humanitarian and communal obligation, the societal advantage of milk repositories, contribution endorsement, and willingness for voluntary participation. Dimension loadings spanned 0.646 to 0.880, with Cronbach alpha coefficient of 0.943.

Dimension 2 (Informational and Security Consciousness) possessed a characteristic value of 2.280 and accounted for 20.660% of variance. Statements within this dimension appraised fundamental knowledge concerning donor milk banking, consciousness regarding control of infectious pathology throughout contribution, and security-related consciousness. Dimension loadings spanned 0.703 to 0.891, with Cronbach alpha coefficient of 0.874.

Dimension 3 (Personal Evaluations and Reservations) possessed a characteristic value of 1.412 and accounted for 13.632% of variance. This dimension encompassed individual assessments, hesitations, and restrictive perspectives concerning breast milk contribution. Dimension loadings spanned 0.530 to 0.847, with Cronbach alpha coefficient of 0.655, situated at the lower acceptability boundary yet adequate for the development of preliminary-stage instruments.

Analysis of Structural Verification

Analysis of structural verification was performed on an autonomous sample to corroborate the tripartite configuration identified through dimension reduction.

Table 3. Results of exploratory factor analysis	
Factors/items	**Loading**
Factor 1: Social Support and Behavioral Intention (Eigenvalue=8.925, Var=35.80%, a=0.943)	
PAT-HMBS14: Breast milk donation is positively regarded in Turkish culture	0.880
PAT-HMBS17: Establishing milk banks is beneficial for society	0.797
PAT-HMBS23: I could encourage family/friends to donate milk	0.769
PAT-HMBS13: Milk donation can be made considering religious precautions	0.765
PAT-HMBS18: Mothers who donate milk should be appreciated	0.764
PAT-HMBS21: I would consider donating my milk to another baby	0.757
PAT-HMBS22: I would accept using donated milk for my baby	0.748
PAT-HMBS24: I would voluntarily contribute to milk donation projects	0.700
PAT-HMBS16: Breast milk donation is a humanitarian responsibility	0.697
PAT-HMBS19: Government policies should promote milk donation	0.682
PAT-HMBS12: Breast milk donation is religiously permissible	0.646
Factor 2: Knowledge and Safety Awareness (Eigenvalue=2.280, Var=20.66%, a=0.874)	
PAT-HMBS4: I am aware that medical tests are performed for safety	0.891
PAT-HMBS3: I know infectious diseases can be controlled through screening	0.859
PAT-HMBS2: I have heard of human milk banking before	0.836
PAT-HMBS1: I know milk donation is vital for babies without breast milk	0.703
Factor 3: Individual Perceptions and Hesitations (Eigenvalue=1.412, Var=13.63%, a=0.655)	
PAT-HMBS7: Donor breast milk is safer than formula	0.847
PAT-HMBS9: Milk donation can be safely done under proper storage	0.816
PAT-HMBS5: Milk donation is only for preterm and sick babies	0.530
Total Variance Explained =70.089%, Overall Cronbach alpha=0.925	

The model encompassed three latent constructs: Communal Encouragement and Behavioral Inclination (F1), Informational and Security Consciousness (F2), and Personal Evaluations and Reservations (F3), with their corresponding manifest indicators.

Model correspondence indices signified satisfactory fit: χ^2/df=1.818 (satisfactory range: 0-5), RMR=0.028, GFI=0.892, NFI=0.927, RFI=0.915, IFI=0.966, TLI=0.960, CFI=0.965, and RMSEA=0.064 (Figure 1). All standardized dimension loadings achieved statistical significance ($p<0.001$): Dimension 1 loadings spanned 0.772 to 0.904, Dimension 2 loadings spanned 0.799 to 0.882, and Dimension 3 loadings spanned 0.872 to 0.881 (Tables 3, and 4, Figure 1).

Discriminative Capacity

To appraise discriminative capacity of the instrument, independent sample comparisons were undertaken between lowest 27% and highest 27% subgroups based upon cumulative scores. Outcomes revealed statistically significant intergroup differences in cumulative instrument scores and all subscale scores (t=-6.99 to -18.75, all $p<0.001$), signifying that the instrument possesses robust discriminative capacity at both aggregate and subscale levels.

Temporal Consistency

Temporal consistency underwent assessment to scrutinize instrument measurement stability. Paired sample comparisons did not signify any statistically significant differences between initial and repeated administration scores for the cumulative instrument or any subscale (all $p>0.05$). ICC spanned 0.91 to 0.93 and all achieved statistical significance ($p<0.001$) demonstrating superior temporal consistency at both aggregate and subscale levels.

Descriptive Findings for Instrument and Subscale Scores

Mean cumulative instrument scores of participants were computed as 33.54±11.50 (minimum: 18, maximum: 90), and 19.320±7.780 (minimum: 11, maximum: 55) within the communal encouragement behavioral inclination subdomain, 8.170±3.722 (minimum: 4, maximum: 20) within Informational Security Consciousness, and 6.050±2.403 (minimum: 3, maximum: 15) the Personal

Table 4. Model fit indices			
Fit index	**Value**	**Acceptable range**	**Reference**
Chi-square	236.329	-	-
df	130	-	-
Chi-square/df	1.818	0-5	Kline[13]
RMR	0.028	0.05-0.08	Hooper et al.[12]
GFI	0.892	0.80-0.95	Kline[13]
NFI	0.927	0.90-1.00	Hu and Bentler[30]
RFI	0.915	0.90-1.00	Hu and Bentler[30]
IFI	0.966	0.80-1.00	Hooper et al.[12]
TLI	0.960	0.80-1.00	Hooper et al.[12]
CFI	0.965	0.90-1.00	Hu and Bentler[30]
RMSEA	0.064	0.05-0.08	Hu and Bentler[30]

Df: Degree of freedom, RMR: Root Medan Square Residual, GFI: Goodness-of-Fit Index¸ NFI: Normed Fit Index, RFI: Relative Fit Index, IFI: Incremental Fit Index, TLI: Tucker-Lewis Index, CFI: Comparative Fit Index, RMSEA: Root Mean Square Error of Approximation

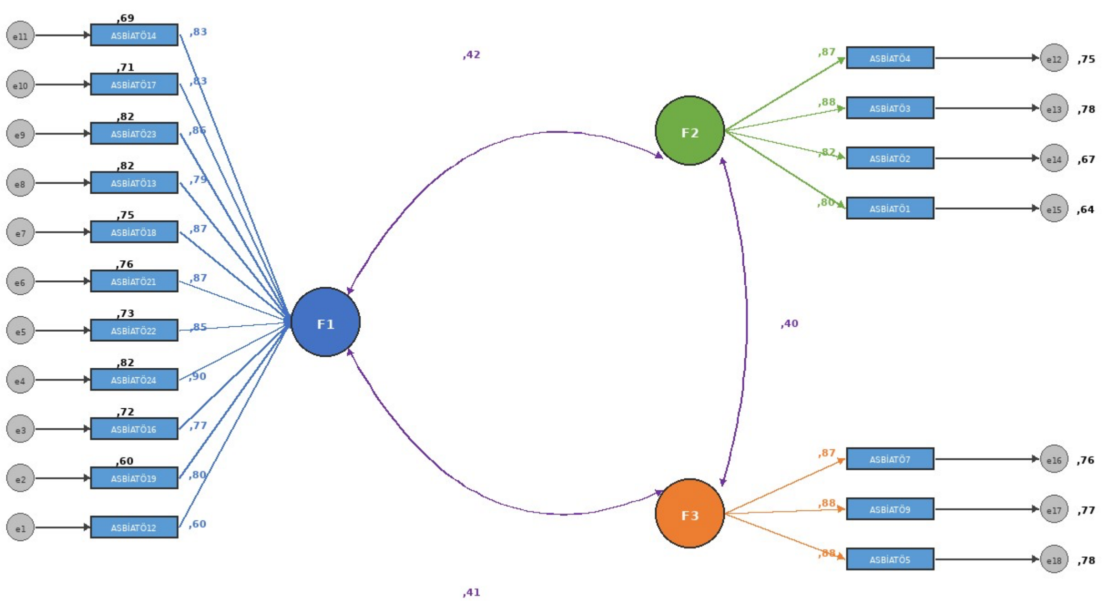

Figure 1. Path diagram of confirmatory factor analysis

Evaluations Reservations subdomains. These findings signify that perspectives and attitudes of participants toward donor milk banking are generally situated at diminished-to-moderate levels (Supplementary Table).

DISCUSSION

This investigation was undertaken to construct the PAT-HMBS and comprehensively appraise its measurement characteristics. The preliminary Cronbach coefficient alpha of 0.872 signified that statements consistently represented the assessed construct and exhibited satisfactory homogeneity. Coefficient alpha values ≥0.80 were regarded as indicators of elevated reliability[22,23]. This finding suggests that the instrument constitutes an appropriate measurement- tool for capturing perspectives and attitudes toward donor milk services (Supplementary Table).

Analysis of items disclosed that certain statements exhibited minimal or inverse adjusted statement-scale correlations, signifying inadequate correspondence with the assessed construct. Statement-scale correlations beneath 0.30 furnish robust justification for statement elimination[24,25]. The elevation in Cronbach alpha up to 0.925 subsequent to elimination of these statements demonstrates substantially fortified homogeneity and enhanced measurement precision[23,25].

Sampling appropriateness for factorization was corroborated by the KMO coefficient (0.789) and statistically significant Bartlett's sphericity test results, signifying that structure information was suitable for dimensional decomposition[10,26]. The tripartite configuration from dimension reduction accounted for 70.089% of cumulative variance, surpassing the 60% threshold advocated for behavioral science investigations which also signifies robust structural validity[11,24].

Scrutiny of subscales disclosed that the elevated variance accounted (35.797%) and superior homogeneity (α=0.943) of Dimension 1 signified that Communal Encouragement and Behavioral Inclination constitutes the central constituent of this assessment instrument. This finding aligns with behavioral theoretical frameworks suggesting that contribution behaviors are intimately associated with communal propensities and perceptions of societal obligation[11,27]. The robust dimension loadings and elevated reliability (α=0.874) of Dimension 2 established that Informational and Security Consciousness constitutes an autonomous and distinguishable cognitive dimension[10,28]. Despite Dimension 3 exhibiting diminished variance (13.632%) and acceptable homogeneity (α=0.655), this level is deemed adequate for preliminary-stage development of this instrument[22,25].

Outcomes of structural verification corroborated that the tripartite measurement model exhibited satisfactory correspondence with observed data. The χ^2/df ratio beneath 2, RMSEA within acceptable boundaries, and elevated CFI, TLI, and IFI values furnished robust evidence for structural validity[11,12,29]. The elevated and statistically significant dimension loadings signified that manifest variables reliably reflected their corresponding latent constructs.

Significant intergroup differences detected during discriminative analyses between lowest and highest 27% subgroups demonstrated elevated sensitivity in differentiating individual variations[24,30]. Furthermore, elevated ICC values (0.909-0.925) derived from temporal consistency analyses signified that the instrument yields stable measurements across time and demonstrated robust temporal reliability[31,32]. These comprehensive findings establish that the PAT-HMBS possesses elevated measurement quality concerning structural validity, discriminative capacity, and reliability, and may be confidently employed within both investigative and clinical contexts.

Study Limitations

This study has several limitations. First, the cross-sectional design precluded establishing causal relationships and assessing temporal stability of attitudes. Second, the sample was recruited from a single geographic region, which may limit generalizability to diverse populations with different cultural or religious perspectives toward donor milk banking. Third, reliance on self-reported data introduced potential social desirability bias.

CONCLUSION

The constructed instrument represents the inaugural psychometrically sound multidimensional tool assessing maternal perspectives and attitudes toward donor milk services in Türkiye, incorporating theological and sociocultural sensitivities pertinent to Muslim communities. It contributes substantially to investigation and practice by guiding developmental processes of culturally appropriate system and also enhancing communal acceptance.

Ethics

Ethics Committee Approval: Ethical authorization was secured from the Amasya University Rectorate–Non-Interventional Clinical Research Ethics Committee on (decision no.: 2025000172, date: 02.10.2025), with institutional clearance obtained from İzmir Bakırçay University Çiğli Training and Research Hospital. All participants received information concerning investigation objectives and methodology, with written authorization secured in accordance with the principles of voluntary participation. The investigation adhered to World Medical Association Declaration of Helsinki–Ethical Principles for Medical Research Involving Human Participants.

Informed Consent: Written informed consent was secured from all participants.

Footnotes

Author Contributions

Concept: Ş.K.E., A.M., E.C.E., Design: Ş.K.E., A.M., E.C.E., Data Collection or Processing: A.M., Ö.O., Analysis or Interpretation: Ş.K.E., A.M., E.C.E., Literature Search: Ş.K.E., A.M., E.C.E., Writing: Ş.K.E., A.M., E.C.E.

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Supplementary Table: https://d2v96fxpocvxx.cloudfront.net/68ab204c-182b-49da-b227-bc7efe058632/content-images/d7105213-0425-4bf2-a463-ddbd52f03dde.pdf

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Original Article

Central Tegmental Tract Hyperintensity on Cranial MRI in Pediatric Patients

Pediatrik Hastalarda Kraniyal MRG'de Santral Tegmental Trakt Hiperintensitesi

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ABSTRACT

Objective: The central tegmental tract (CTT) is an extrapyramidal pathway located in the brainstem. CTT hyperintensity (CTTH) is a neuroimaging finding of uncertain etiology, considered either part of the normal maturation process or a finding that can be seen in various neurological conditions. This study aims to investigate its relationship with age and the associated disorders of CTTH observed in the pediatric population.

Method: All brain magnetic resonance imagings (MRIs) performed between July 2023 and November 2025 at a tertiary pediatric hospital were retrospectively reviewed. Eighty-one pediatric patients with CTTH were included in the study. Clinical data, additional MRI findings, and available follow-up scans were examined.

Results: CTTH was detected in 1.4% of all cranial MRIs, while the median age of the cases was 17 months. The most common complaints at admission were seizures (35.8%) and developmental delay (28.4%). Additional MRI findings (most commonly periventricular leukomalacia) were observed in 51.9% of the cases. The age of patients in this group with additional MRI findings was significantly lower than those without (median ages: 15 vs. 23 months). CTTH resolved in 36.7%, and persisted in 63.3% of the patients who underwent follow-up MRI. It was determined that CTTH resolved significantly in older children compared to the persistent cases among younger patients (median: 26 vs. 14 months).

Conclusion: CTTH is a finding that can be seen in pediatric cranial MRI examinations, and its clinical significance should be interpreted by considering the patients' age and associated neurological conditions.

Keywords: Central tegmental tract hyperintensity, cranial MRI, pediatric neuroimaging, cerebral palsy, myelination

ÖZ

Amaç: Santral tegmental trakt (STT), beyin sapında yer alan ekstrapiramidal bir sinir yoludur. STT hiperintensitesi (STTH), etiyolojisi belirsiz bir nörogörüntüleme bulgusu olup, normal matürasyonun bir parçası veya nörolojik hastalıklarda görülebilen bir bulgu olarak değerlendirilmektedir. Bu çalışma, pediatrik popülasyonda görülen STTH'nin yaş ile ilişkisini ve eşlik eden hastalıkları araştırmayı amaçlamaktadır.

Yöntem: Temmuz 2023-Kasım 2025 tarihleri arasında bir üçüncü basamak çocuk hastanesinde çekilen tüm beyin MRG'ler retrospektif olarak tarandı. STTH saptanan 81 pediatrik olgu çalışmaya dahil edildi. Olguların klinik verileri, ek MRG bulguları ve mevcut takip görüntülemeleri analiz edildi.

Bulgular: Kraniyal MRG'lerin %1,4'ünde STTH tespit edildi; olguların ortanca yaşı 17 aydı. En sık başvuru şikayetleri nöbet (%35,8) ve gelişim geriliği (%28,4) olarak saptandı. Olguların %51,9'unda ek MRG bulgusu (en sık periventriküler lökomalazi/asfiksi sekeli) görüldü; bu gruptaki hastaların yaşı ek bulgusu olmayanlara göre anlamlı düzeyde daha düşüktü (medyan: 15 vs. 23 ay). Takip MRG'si yapılanların %36,7'sinde STTH'nin kaybolduğu, %63,3'ünde sebat ettiği görüldü. Bulgunun kaybolduğu olguların, sebat edenlere göre anlamlı şekilde daha büyük yaşta olduğu (medyan: 26 vs. 14 ay) belirlendi.

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Sonuç: STTH, pediatrik kraniyal MRG incelemelerinde görülebilen ve klinik önemi hasta yaşı ile eşlik eden nörolojik durumlar dikkate alınarak yorumlanması gereken bir bulgudur.

Anahtar kelimeler: Santral tegmental trakt hiperintensitesi, kraniyal MRG, pediatrik nörogörüntüleme, serebral palsi, myelinizasyon

INTRODUCTION

Central tegmental tract (CTT) is an extrapyramidal pathway that runs along the posterior brainstem and connects the red nucleus in the mesencephalon to the inferior olivary nucleus in the medulla. On routine brain magnetic resonance imaging (MRI), the CTT is usually not identified as a distinguishable signal. However, in certain cases, it may appear as a symmetrical area of hyperintensity within the pontine tegmentum, particularly on T2-weighted and diffusion-weighted sequences[1,2].

CTT hyperintensity (CTTH) is a relatively rare neuroimaging finding with an unclear etiology. Some studies have suggested that CTTH observed in early childhood may represent a component of the normal myelination process[3]. Kesimal et al.[4] proposed that CTTH may be related to physiological maturation, while also potentially occurring secondary to a transient response of brain tissue to toxic, metabolic, or ischemic injury. In addition, CTTH has been reported in association with various neurological conditions, including cerebral palsy, epilepsy, developmental delay, and intracranial tumors[1,5-7]. Conversely, a more recent study suggested that CTTH may reflect irreversible myelin degeneration[8].

The conflicting literature data indicate that the pathophysiology of CTTH remains incompletely understood. The objectives of this study are to determine the prevalence of CTTH and its relationship with age, to identify associated neurological conditions, and to evaluate the presence of concomitant cranial abnormalities. In addition, we investigated whether CTTH persists on follow-up imaging and examined its association with patient's age.

MATERIALS and METHODS

Patient Selection

This retrospective and descriptive study included a review of all brain scans performed between July 2023 and November 2025 at a tertiary referral pediatric hospital ie. Ethical approval was obtained from the University of Health Sciences Türkiye, Dr. Behçet Uz Children's Diseases and Surgery Training and Research Hospital (decision no.:2026/01-07, date: 15.01.2026). All brain MRI reports were retrospectively screened, and all pediatric patients (0-18 years) in whom CTTH was identified were included in the study. The prevalence of CTTH was calculated. In patients with follow-up MRI scans, the persistence or resolution of CTTH on control MRIs was recorded. Patients in whom CTTH could not be reliably evaluated due to motion artifacts or insufficient image quality (n=3), as well as those whose clinical data could not be accessed through hospital medical records (n=1), were excluded from the study.

Clinical and Demographic Data

Sex and age of the patients at the time of MRI examination were recorded for all patients. Perinatal data were obtained from the hospital information system. Patients with a gestational age of ≥37 weeks were classified as term, and those born at <37 weeks as preterm infants. A history of neonatal intensive care unit (NICU) admission and, if present, the duration of hospitalizastion were recorded. The presence of motor deficits at presentation, Denver Developmental Screening Test results, and electroencephalography (EEG) findings were retrieved from hospital records. EEG findings showing slowing, dysmaturation, epileptiform activity, or other pathological patterns were categorized as "pathological EEG".

The primary presenting complaints and pre-MRI preliminary diagnoses were recorded. In addition, information regarding final diagnoses and confirmed genetic or metabolic disorders, if present, was obtained from hospital records and review of the archival data.

MRI Protocol and Image Analysis

Cranial MRI examinations were performed using a 1.5 Tesla scanner (Philips Ingenia, Philips Healthcare, Best, The Netherlands). CTTH was assessed on diffusion-weighted images (b=0 and 1000 s/mm^2), axial T2-weighted images, and T2-weighted fluid-attenuated inversion recovery sequences. All images were evaluated by a single neuroradiologist with 10 years of experience in pediatric neuroimaging. Imaging parameters of the three sequences used for the assessment of CTTH are provided in Table 1. Additional findings potentially associated with CTTH were evaluated considering all MRI sequences. The routine brain MRI protocol consisted of axial T1W, T2W, T2-FLAIR, diffusion weighted imaging (DWI), sagittal T1W, and coronal T2W sequences.

Hyperintensity along the course of the CTT within the pontine tegmentum on T2-weighted and/or DWI sequences was defined as CTTH (Figure 1). Signal abnormalities and pathological findings in other neural pathways and anatomical regions of the brain were also recorded. For patients with available follow-up MRI scans, sex, age at follow-up MRI, and the interval between the initial and follow-up MRI examinations were calculated.

Statistical Analysis

Statistical analyses were performed using SPSS version 20 software. A two-tailed p value of <0.05 was considered statistically significant.

Statistical comparisons of sex and age of the patients with and without additional MRI findings were conducted using Fisher's exact test for categorical and the Mann-Whitney U test for continuous variables. The interval between the initial and follow-up MRI examination results were compared between patients with persistent and resolved CTTH using the Mann-Whitney U test. Comparisons of sex and age between patients with and without signs of CTTH detected on follow-up MRI scans were performed using Fisher's exact test and the Mann-Whitney U test, respectively.

RESULTS

The study population (n=81) consisted of 34 (42%) female, and 47 (58%) male patients. Patients' ages ranged from 2 to 131 months, with a mean age of 22.3±18.3 months and a median age of 17 months (25th percentile, 12 months; 75th percentile, 28.5 months). The estimated prevalence of CTTH was 1.4% (81/5,810) considering all cranial MRI examinations performed during the study period. Based on gestational age, 13 (16%) patients were classified as preterm and 68 patients (84%) as term infants. Twenty-three patients (28.4%) had a history of NICU admission, with a mean duration of 24±24 days. Motor deficits were observed in 11 (13.6%) patients at presentation. Developmental delay was detected in 29 (58%) out of 50 patients who underwent the Denver Developmental Screening Test, and pathological findings were detected on EEGs of 17 (43.6%) out of 39 patients (Table 2).

Table 1. Imaging parameters of the MRI sequences

Parameters	T2 axial	DWI	FLAIR
TR (ms)	4000	4698	11000
TE (ms)	110	97	140
Slice thickness (mm)	4	4	4.2
FOV (mm)	230	194	230
NEX	1	2	1
Acquisition time (s)	136	98	176

TR (ms): Repetition time in milliseconds, TE: Echo time in milliseconds, MRI: Magnetic resonance imaging, FOV: Field of view in millimeters, NEX: Number of excitations

The primary presenting complaints were detected in indicated number of patients as follows: seizures (n=29), developmental delay (n=23), fever (n=4) (suspected central nervous system infection), hypotonia (n=4), movement disorders (n=4), visual symptoms (n=4), behavioral changes (n=4), macrocephaly (n=4), microcephaly (n=1), facial paralysis (n=1), trauma (n=1), suspected diagnoses of Langerhans cell histiocytosis (n=1), and neurofibromatosis (n=1).

Pre-MRI preliminary diagnoses included epilepsy (n=21), asphyxia (n=18), genetic or metabolic disorders (n=14), encephalitis/encephalopathy/infection (n=13), suspect cases of hemorrhage or mass lesion (n=9), and conditions potentially associated with neurodevelopmental disorders in 6 patients. Definitive genetic and metabolic diagnoses are summarized in Table 3.

While no additional MRI findings were observed in 39 patients, 42 (51.9%) patients demonstrated additional findings accompanying CTTH (Figure 2). In 16 patients, symmetrical and bilateral signal hyperintensities were observed in other cerebral regions on diffusion-weighted images including: isolated inferior cerebellar peduncles in 5, isolated fornix in 5, fornix + globus pallidus + hippocampus in 2, fornix + mammillary body + hippocampus in 2, isolated hippocampus in 1, and fornix + hypothalamus in 1 patient, respectively. Additional findings included periventricular leukomalacia/asphyxia-related changes in 12, thinning of the corpus callosum in 3, arachnoid cyst in 3, hydrocephalus in 2, septo-optic dysplasia in 2, subependymal heterotopia in 1, cortical tuber in 1, quadrigeminal lipoma in 1, and subarachnoid hemorrhage in 1 patient, respectively.

There were no statistically significant gender differences between patients with and without additional MRI findings (p=0.368). The median age of the patients without and with additional MRI findings was 23 months (25th percentile, 13 months; 75th percentile, 33 months) and 15 months (25th percentile, 10.8 months; 75th percentile, 22 months), respectively, with a statistically significant difference between the groups (p=0.027).

Follow-up MRI scans were available for 30 (37%) patients. The mean interval between the initial and follow-up MRI examinations was 13.5±20.3 months. When follow-

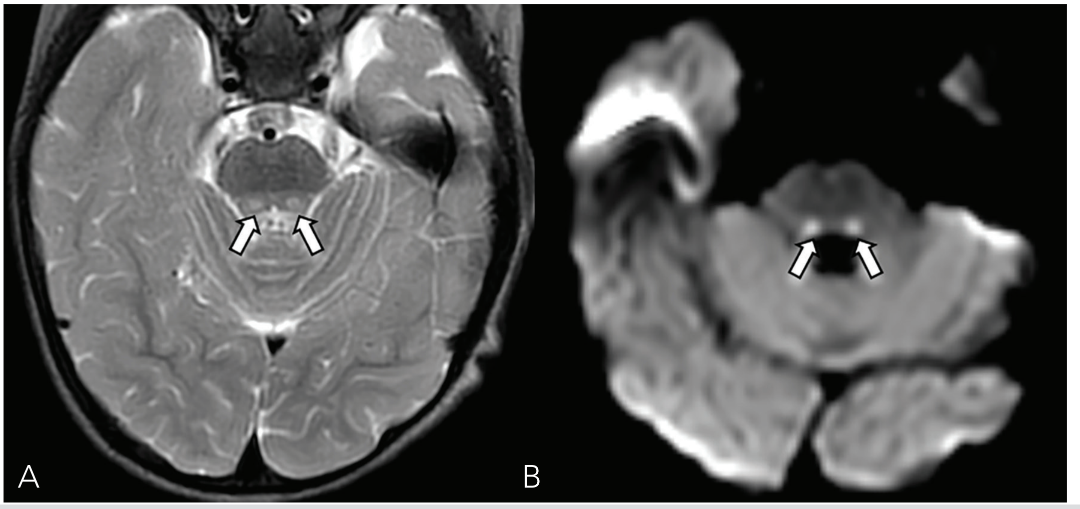

Figure 1. In a 16-month-old male patient followed for mitochondrial disease, central tegmental tract hyperintensity is demonstrated on (A) T2-weighted imaging and (B) diffusion-weighted MRI (arrows)

MRI: Magnetic resonance imaging

Table 2. Demographic and clinical characteristics of the cases

Total number of cases	**81**
Age (months), median	17 (25p 12; 75p 28.5) months
Age (months), mean (minimum-maximum)	22.3 (2-131) months
n (%)	
Female patients	34 (42)
Male patients	47 (58)
Term infants	68 (84)
Preterm infants	13 (16)
No NICU admissions	58 (71.6)
NICU admissions present	23 (28.4)
Past history of seizure	50 (64.2)
Patients with seizure	29 (35.8)
Normal development	21 (42)
Isolated motor delay	4 (8)
Isolated cognitive/language delay	8 (16)
Global developmental delay	17 (34)
Developmental assessment was not performed	31 (38)
Normal EEG	22 (56.4)
Pathological EEG	17 (43.6)
EEG not performed	42 (51)
Patients without genetic disorder	61 (75.3)
Patients with genetic disorder	20 (24.7)

EEG: Electroencephalography, NICU: Neonatal intensive care unit

up MRI scans were examined, it was seen that CTTH had resolved in 11 (36.7%) and persisted in 19 (63.3%) patients. There was no significant difference in terms of the follow-up intervals between patients with resolved and persistent CTTH (p=0.11). No significant difference was observed on follow-up MRI scans regarding the distribution of male and female patients with and without CTTH (p=0.1). The median age of patients without and with CTTH on follow-up MRI scans was 26 months (25th percentile, 21 months; 75th percentile, 35 months) and 14 months (25th percentile, 5 months; 75th percentile, 20 months), respectively, with a statistically significant difference between the groups in terms of median ages of the patient groups (p=0.003).

DISCUSSION

The results of our study performed in the pediatric population have demonstrated that CTTH is associated with a heterogeneous clinical spectrum that shows variability with age. The median age of the 81 patients included in the study was 17 months. One of the most notable findings was that patients with additional MRI abnormalities were significantly younger (median age, 15 months) than those without (median age, 23 months) (p=0.027). Furthermore, the finding that patients in whom CTTH resolved on follow-up MRI scans were older (median age, 26 months) than those in whom CTTH persisted (median age, 14 months) (p=0.003), which suggests that CTTH may be a maturation-related and potentially transient phenomenon.

Previous studies have reported a wide spectrum of clinical presentations and indications for imaging in

Table 3. Patients with CTTH and confirmed genetic and metabolic diagnoses

Diagnosis	n
Glutaric aciduria type 1	2
Mitochondrial disease	2
Septo-optic dysplasia	2
FOXC1 mutation	1
L-2-hydroxyglutaric aciduria	1
Neurofibromatosis type 1	1
Greig cephalopolysyndactyly syndrome	1
Achondroplasia	1
Poretti-Boltshauser syndrome	1
Thiamine-biotin-responsive basal ganglia disease	1
Tuberous sclerosis	1
Total**	14

**Six patients whose clinical and/or imaging findings were compatible with a neurometabolic disorder but in whom a definitive genetic or metabolic diagnosis had not been established at the time of the study were not included in this table.
FOXC1 mutation: a genetic defect in the *FOXC1* gene on chromosome 6
CTHH: Central tegmental tract hyperintensity

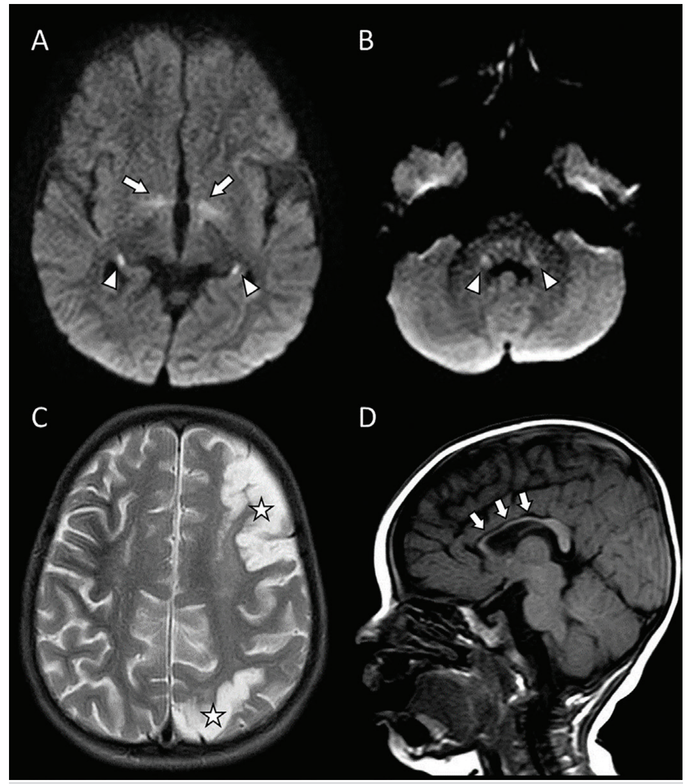

Figure 2. Examples of MRI findings accompanying CTTH. **A)** Bilateral signal increase in the posterior crus of the fornix-hippocampus (arrowheads) and hypothalamus (arrows) on diffusion MRI, **B)** Symmetrical signal increase in the inferior cerebellar peduncles (arrowheads) on diffusion MRI, **C)** Areas of gliotic encephalomalacia (stars) secondary to an old left frontoparietal infarct in a case of cerebral palsy on T2W imaging, and **D)** Thinning of the genu and body of the corpus callosum (arrows) on sagittal T1W imaging

MRI: Magnetic resonance imaging

patients with CTTH[1,3,9]. Dablan et al.[10] reported seizures (40.3%) and developmental delay (15.5%) as the most common presenting complaints in patients with CTTH. In addition, hypotonia, macrocephaly, and movement disorders have also been described as frequent indications for imaging[1,4,9]. In our study, in line with the existing literature data, seizures (35.8%) and developmental delay (28.4%) were the most common presenting complaints of patients with CTTH.

One widely accepted hypothesis is that CTTH occurs in the context of hypoxic-ischemic encephalopathy, in patients receiving vigabatrin for the treatment of West syndrome, and in metabolic conditions such as glutaric aciduria type 1 or mitochondrial disorders[3,7,11,12]. CTTH has also been reported in rare metabolic conditions, including Tay-Sachs disease, Krabbe disease, and *CLCN2*-related leukoencephalopathy[1,13,14]. In our cohort, 22% of patients had a diagnosis of asphyxia. The most frequently confirmed genetic–metabolic diagnoses were glutaric aciduria type 1 and mitochondrial disorders. The coexistence of rare genetic or syndromic conditions, such as *FOXC1* mutations, Greig cephalopolysyndactyly syndrome, and Poretti-Boltshauser syndrome, further suggests that CTTH may be observed across a broad spectrum of neurogenetic disorders.

Common MRI findings reported in association with CTTH include periventricular leukomalacia, thinning of the corpus callosum, and signal abnormalities in the basal ganglia[1,5,15]. Işık and Dinçer[9] described diffuse T2 hyperintensity in the fornix, optic nerves, and basal ganglia accompanying CTTH in a patient with mitochondrial disease. In our study, additional MRI findings were detected in 51.9% of patients, while periventricular leukomalacia/asphyxia-related changes were the most frequently detected comorbidities in 14.8% of the patients. Thinning of the corpus callosum was observed in 3.7% of patients. Notably, 19.8% of patients demonstrated symmetrical and bilateral hyperintensities on diffusion-weighted images involving one or more regions, including the fornix, inferior cerebellar peduncle, hippocampus, hypothalamus, mammillary bodies, and globus pallidus. These accompanying pathologies suggest that CTTH may not represent an isolated brainstem abnormality, but rather it accompanies a more widespread involvement affecting the limbic system and other extrapyramidal pathways.

In their large series of 206 patients, Dablan et al.[10], reported regression of CTTH at a median age of 52 months in 28.6% of their patients as detected on follow-up imaging. Buyukceran et al.[8] reported resolution of CTTH in 58% of patients on follow-up imaging, interpreting resolution as a transient developmental phenomenon and persistence as irreversible myelin degeneration. However, no specific age for the onset of resolution was reported. It has been suggested that endogenous factors, such as underlying mitochondrial disease or severe metabolic disorders may contribute to the persistence of CTTH. In our study, CTTH resolved in 36.7% and persisted in 63.3% of the patients as revealed on follow-up MRI scans. Although previous studies suggested that resolution of CTTH may parallel clinical improvement, our findings indicate that age appears to be a key determinant, supporting the hypothesis that CTTH resolves or disappears as the maturation of the rubro-olivary pathways is completed[4].

Study Limitations

This study has several limitations. The single-center design may limit the generalizability of the findings. Due to its retrospective design, clinical and laboratory data were restricted to information available in hospital records, and advanced genetic testing, such as whole-exome sequencing, could not be performed in all patients with developmental delay, precluding definitive etiological diagnoses in some cases. In addition, the lack of follow-up MRI scans in all patients and the non-standardized follow-up intervals limited the ability to draw stronger conclusions regarding the natural history of CTTH. Finally, the absence of histopathological correlation, similar to other studies in the literature, prevents precise elucidation of the cellular correlates of the observed radiological findings.

CONCLUSION

In conclusion, CTTH is an imaging finding that can be detected on pediatric cranial MRI examinations, but its clinical significance remains uncertain. The clinical relevance of CTTH should be interpreted in the context of patient age and accompanying neurological conditions.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the University of Health Sciences Türkiye, Dr. Behçet Uz Children's Diseases and Surgery Training and Research Hospital (decision no.:2026/01-07, date: 15.01.2026).

Informed Consent: This is a retrospective study.

Footnotes

Author Contributions

Concept: Y.K.Ç., B.M., M.C., Design: Y.K.Ç., B.S.B., M.C., Data Collection or Processing: Y.K.Ç., S.P., B.S.B., D.K.A., B.M., Analysis or Interpretation: Y.K.Ç., S.P., M.C., Literature Search: Y.K.Ç., S.P., D.K.A., B.M., Writing: Y.K.Ç., M.C.

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Original Article

Cardiac Troponin T and Intravenous Immunoglobulin in the Diagnosis and Follow-up of Childhood Myocarditis

Çocukluk Çağı Miyokarditinin Tanı ve İzleminde Kardiyak Troponin T ve İntravenöz İmmünoglobulin

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ABSTRACT

Objective: Our aim was to investigate the therapeutic efficacy of intravenous immunoglobulin (IVIG) in pediatric patients with elevated cardiac troponin T (cTnT) levels and diagnosed with myocarditis confirmed by cardiac magnetic resonance imaging or clinically assessed as probable myocarditis (PM).

Method: We retrospectively reviewed 105 children (mean age 13.4±3.1 years; 81% male) hospitalized with PM between January 2013 and April 2025. Patients were classified as those whose diagnosis of myocarditis was confirmed using cardiovascular magnetic resonance (CMR-confirmed) or PM based on Lake Louise diagnostic criteria. Data concerning demographic features, electrocardiography (ECG), echocardiography, CMR, baseline and follow-up cTnT (Roche high-sensitivity assay; 99th-percentile 0.014 ng/dL), time to normalization of cTnT levels, and IVIG therapy (400 mg/kg/day up to 5 days) were analyzed.

Results: CMR abnormalities were found in 44 (41.9%) patients. Median baseline cTnT level was 0.135 ng/dL (range 0.016-9.057) and median normalization of cTnT levels was achieved within median period of 5 days (range: 2-42 days). IVIG was administered to 38 (36.2%) patients and more often patients with confirmed myocarditis (CM) received IVIG therapy rather than cases with PM (50% vs. 24.5%). Pathologic ECG findings were detected in 32% of all study participants and more frequently in IVIG-treated patients. Troponin normalization rate was slower in IVIG-treated patients (median: 10 vs 6 days), especially in patients with CM. Echocardiographic outcomes and recovery of left-ventricular systolic function had not shown any significant differences between IVIG-treated and untreated groups.

Conclusion: Serum cTnT is a useful adjunct for diagnosis and follow-up of patients with pediatric myocarditis. IVIG was more often used in clinically severe cases but showed no significant effect on recovery of ventricular function or on fluctuations in troponin levels. Larger multicenter studies should be conducted to clarify therapeutic benefit of IVIG.

Keywords: Intravenous immunoglobulin, myocarditis, pediatrics, troponin T

ÖZ

Amaç: Troponin T düzeyi yüksek, kardiyak manyetik rezonans (kMR) ile doğrulanmış veya klinik olarak olası miyokardit (PM) tanısı alan pediatrik hastalarda intravenöz immünoglobulinin (IVIG) tedavi etkinliğini değerlendirme amaçlanmıştır.

Yöntem: 2013-2025 yılları arasında PM nedeniyle yatırılan 105 çocuk (ortalama yaş 13,4±3,1 yıl; %81 erkek) geriye dönük incelendi. Hastalar Lake Louise kriterlerine göre kMR-doğrulanmış miyokardit (CM) veya PM olarak sınıflandırıldı. Demografik veriler, EKG, ekokardiyografi, kMR, seri troponin T düzeyleri ve IVIG tedavisi (400 mg/kg/gün, en fazla 5 gün) analiz edildi.

Bulgular: kMR bulguları 44 hastada (%41,9) pozitiftir. Ortanca başlangıç troponin düzeyi 0,135 ng/dL olup normale dönüş süresi 5 gündü. IVIG 38 hastaya (%36,2) uygulanmış ve CM grubunda daha sık kullanılmıştır. Patolojik EKG bulguları IVIG alanlarda daha yaygındı. Troponin normalizasyonu IVIG alanlarda daha yavaştı, özellikle CM grubunda. Sol ventrikül fonksiyonlarının düzelmesi açısından IVIG alan ve almayan gruplar arasında fark yoktu.

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Sonuç: Troponin T, pediatrik miyokarditin izleminde yararlı bir belirteçtir. IVIG daha ağır olgularda tercih edilmesine rağmen klinik gidiş veya troponin düşme süresi üzerinde anlamlı bir etkisi gösterilememiştir. IVIG'in etkinliğini belirlemek için daha geniş çalışmalara ihtiyaç vardır.

Anahtar kelimeler: İntravenöz immünoglobulin, miyokardit, pediatrik, troponin T

INTRODUCTION

Pediatric myocarditis is an inflammatory disease of the myocardium with a broad clinical spectrum ranging from mild chest pain to severe heart failure and life-threatening arrhythmias. In pediatric patients, viral infections represent the most common etiological factors, with parvovirus B19 and human herpesvirus type 6 among the most frequently reported pathogens[1].

Although endomyocardial biopsy is considered the gold standard for the definitive diagnosis of myocarditis, its routine use in children is limited due to procedural risks and the patchy distribution of myocardial inflammation, which may lead to sampling error and false-negative results. Therefore, in clinical practice the diagnosis of suspected myocarditis is generally based on the combined evaluation of clinical findings, biochemical markers, electrocardiographic (ECG) abnormalities, and results of non-invasive imaging techniques such as echocardiography and cardiac magnetic resonance imaging (CMRI)[2].

CMRI has become an important tool in the non-invasive evaluation of myocarditis. The updated Lake Louise diagnostic criteria support the diagnosis of myocardial inflammation by integrating T1-based markers of myocardial injury [such as late gadolinium enhancement (LGE) and increased native T1 values] and T2-based markers of myocardial edema[3,4,5].

Cardiac troponins are widely used biomarkers for the assessment of myocardial injury. Cardiac troponin T (cTnT) and cardiac troponin I are specific to myocardial tissue, and their elevation in serum reflects cardiomyocyte damage. Elevated troponin levels are frequently observed in pediatric myocarditis and are considered supportive evidence of myocardial injury; however, inconsistent literature data has been reported on the causal relationship between troponin levels and disease severity or prognosis[6,7,8].

Although no universally accepted specific therapy exists for myocarditis, intravenous immunoglobulin (IVIG) is commonly used in pediatric clinical practice. IVIG is thought to reduce myocardial inflammation through viral neutralization and modulation of cytokine activity. However, evidence regarding its clinical efficacy in pediatric myocarditis remains inconsistent[9,10,11].

In this study, we aimed to evaluate the clinical utility of cTnT as a supportive biomarker in the diagnosis and follow-up of pediatric patients hospitalized with suspected myocarditis. In addition, we investigated the relationship between IVIG treatment and clinical course in two groups of patients classified separately as having confirmed myocarditis (CM) and clinically suspected (probable) myocarditis.

MATERIALS and METHODS

This retrospective single-center study was conducted at a tertiary pediatric referral center. Ethical approval for the study was obtained from the institutional ethics committee of University of Health Sciences Türkiye İzmir Faculty of Medicine Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital (decision no.: 2025/14-12, date: 11.09.2025).

The medical records of pediatric patients hospitalized with a preliminary diagnosis of myocarditis between January 2013 and April 2025 were retrospectively reviewed. Data concerning demographic characteristics of the patients, physical examination, ECG, transthoracic echocardiographic, CMRI findings, baseline and follow-up cTnT levels, time to troponin normalization, and the administration of IVIG therapy were recorded.

Since CMRI was not available at our center before 2013, as cTnT assay Roche high-sensitivity troponin T test, with the 99th percentile upper reference limit defined as 0.014 ng/dL was used in this study, and patients admitted prior to that date were excluded from the study.

Patients with other clinical conditions that could cause troponin elevation including cardiomyopathies, muscular dystrophy, sepsis-related secondary cardiac dysfunction, significant valvular heart disease, congenital heart disease with ventricular dysfunction, and cardiac involvement secondary to systemic rheumatologic diseases were excluded.

Left ventricular systolic function was assessed via two-dimensional transthoracic echocardiography using the Simpson biplane method. An ejection fraction below 55% was considered indicative of systolic dysfunction. Although diastolic function was evaluated using transmitral Doppler and tissue Doppler parameters, these data were not included in the statistical analysis due to incomplete documentation. Strain echocardiography was performed in some patients. However since a standardized protocol was not consistently applied during the study period, these relevant data were not systematically analyzed.

CMRI examinations were performed within the first week of hospitalization. CMRI was conducted using a 1.5-Tesla magnetic resonance imaging (MRI) scanner. The imaging protocol included cine, T1-and, T2-weighted sequences, and LGE imaging following administration of gadolinium as contrast agent. Gadolinium contrast agent was intravenously administered to all patients, and LGE imaging was evaluated in all cases. ECG synchronization was used for the monitoring of cardiac rhythm during imaging process. In patients with heart rates high enough to potentially compromise image quality, beta-blocker therapy was administered prior to CMR acquisition.

The diagnosis of myocarditis was based on the updated 2018 Lake Louise criteria. Findings indicating myocardial injury on T1-weighted imaging included LGE and increased native T1 values. Myocardial edema detected on T2-weighted imaging was considered indicative of myocardial inflammation. Patients with clinically suspected myocarditis who fulfilled these CMR criteria were classified as having CM. Patients with elevated troponin levels but no CMR abnormalities were classified as having probable myocarditis (PM).

Endomyocardial biopsy is not routinely performed at our center. According to national healthcare regulations, this procedure is performed only in transplant centers; therefore, endomyocardial biopsy could not be performed in this study.

The decision to administer IVIG therapy was made by the attending pediatric cardiologist based on clinical evaluation. IVIG therapy was preferentially administered to patients with markedly elevated troponin levels, persistent chest pain, significant ECG abnormalities, or left ventricular systolic dysfunction. IVIG was administered at a dose of 400 mg/kg/day for up to five days, with a maximum cumulative daily dose of 2 g/kg.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed using the Shapiro-Wilk test. Normally distributed variables were expressed as mean ± standard deviation, while non-normally distributed variables were reported as median (minimum-maximum) values. Categorical variables were presented as numbers and percentages.

Comparisons between groups were performed using the independent samples t-test for normally distributed continuous variables and the Mann-Whitney U test for non-normally distributed variables. Categorical variables were compared using the chi-square test. Time to normalization of troponin levels in patients receiving and not receiving IVIG was compared using the Mann-Whitney U test. A p-value <0.05 was considered statistically significant.

RESULTS

Study population (n=105) hospitalized with suspected myocarditis consisted of 85 (81%) male and 20 (19%) female pediatric patients. The mean age of the study population was 13.4±3.1 years (range: 6-17 years). According to CMRI findings, patients were divided into two separate groups as having CM, and PM. CMRI findings consistent with myocarditis were detected in 44 (41.9%) patients. There were no significant differences between the CM and PM groups in terms of age or sex distribution.

Electrocardiography was normal in 72 (68.6%), and pathological in 33 (31.4%) patients. Among patients with abnormal ECG findings, ST-segment elevation in the anterior leads was detected in 16 (15.2%), ST-segment elevation in the inferior leads in 7 (6.7%). ST-segment depression in the inferior leads in 2 (1.9%) and in the anterior leads in 1 (1%) patient. Pathological T-wave changes were detected in 5 (4.8%), QRS fragmentation in 1 (1%), and supraventricular tachycardia in 1 (1%) patient. A significant association was observed between baseline cTnT levels and the presence of ST-segment elevation. Median cTnT values were markedly higher in patients with ST elevation compared with those without (0.692 vs 0.084 ng/dL, p<0.00001). Pathological ECG findings were more frequently observed in patients receiving IVIG therapy. Nineteen patients in the IVIG group had abnormal ECG findings compared with fifteen patients in the non-IVIG group (p=0.007).

Two-dimensional transthoracic echocardiography was normal in 90 (85.7%). Patients mild mitral regurgitation was detected in 9 (8.6%), pericardial effusion in 2 (1.9%), mild aortic regurgitation in 1 (1%), mitral valve prolapse in 1 (1%), asymptomatic bicuspid aortic valve in 1 (1%), and left ventricular hypertrophy in 1 (1%) patient. No significant differences were observed between the CM and PM groups in terms of echocardiographic findings. Echocardiographic abnormalities were detected in patients receiving (n=9), and not receiving (n=7) IVIG therapy. Besides, statistically significant correlation was not observed between IVIG therapy and echocardiographic findings (p=0.126). One patient with pericardial effusion also had left ventricular systolic dysfunction. Despite IVIG therapy, systolic function progressively deteriorated, and the patient required veno-arterial extracorporeal membrane oxygenation support.

CMRI demonstrated findings consistent with myocarditis in 44 (41.9%) patients. Among these patients, increased T1-weighted MRI signals observed in the lateral wall of the left ventricle in 28 (26.7%) patients. T2-weighted MRI detected myocardial edema in 10 (9.5%), early gadolinium uptake in the interventricular septum in 4 (3.8%), and both early gadolinium uptake and pericardial effusion in 6 (5.7%) and right ventricular dyskinesia in 1 (1%) patient. Based on these findings, patients fulfilling the diagnostic criteria were classified as having CM, whereas patients with elevated troponin levels but without CMR abnormalities were classified as suffering from PM.

The median baseline cTnT level in the entire cohort was 0.135 ng/dL (range: 0.016-9.057 ng/dL). The median time to normalization of troponin levels was 5 days (range: 2-42 days). The median baseline cTnT level was 0.647 ng/dL in 38 (36.2%) patients receiving IVIG therapy (range: 0.026-4.199 ng/dL), and it was 0.488 ng/dL (range: 0.016-9.057 ng/dL) in 67 (63.8%) patients not receiving IVIG therapy

IVIG therapy was administered to 24 patients (50%) in the CM and to 14 patients (24.5%) in the PM group, whereas IVIG was administered at a significantly higher rate in the CM group (p=0.012). The time to normalization of troponin levels was longer in patients receiving IVIG therapy. Troponin levels were normalized after a median of 10 days (range: 3-42 days) in the IVIG group and after a median of 6 days (range: 2-27 days) in the non-IVIG group. Clinical variables according to troponin normalization time are summarized in Table 1. In the subgroup analysis of the CM group, the time to normalization of troponin levels was significantly longer in patients receiving IVIG (p=0.006) therapy, whereas no significant difference was observed in terms of this parameter between those receiving and not receiving IVIG therapy in the PM group (p=0.204). Clinical variables according to troponin T levels and IVIG therapy are summarized in Table 2.

During long-term follow-up period exceeding one year, alternative or evolving diagnoses emerged in some patients. One patient receiving IVIG therapy was diagnosed with restrictive cardiomyopathy during follow-up. Another patient presented six months after discharge with recurrent troponin elevation; repeat CMRs did not reveal findings consistent with active myocarditis, and the persistent troponin elevation was ultimately attributed to macrotroponin positivity. In another patient with recurrent troponin elevations and a family history of cardiomyopathy, genetic testing revealed a desmoplakin (DSP) gene mutation. Serial Holter monitorings demonstrated non-sustained ventricular tachycardia, and follow-up CMR findings were consistent with arrhythmogenic right ventricular dysplasia.

DISCUSSION

In this retrospective study, we evaluated the role of cTnT in the diagnosis and follow-up of pediatric patients hospitalized with suspected myocarditis and

Table 1. Normalization of troponin levels according to IVIG treatment

Baseline cTnT levels (ng/dL)	IVIG (n=38)	No IVIG (n=67)	p-value
Time to normalization of troponin levels (days)	0.647 (0.026-4.199)	0.488 (0.016-9.057)	0.214
Pathological ECG findings, n	10 (3-42)	6 (2-27)	0.006
Echocardiographic abnormalities, n	19	15	0.007
Baseline cTnT levels (ng/dL)	9	7	0.126

IVIG: Intravenous immunoglobulin, ECG: Electrocardiography, cTnT: Cardiac troponin T

Table 2. Clinical characteristics according to troponin T levels and IVIG treatment

Variables	Confirmed myocarditis (n=48)	Probable myocarditis (n=57)	p-value
Baseline cardiac troponin T levels (ng/dL)	0.692 (0.018-9.057)	0.084 (0.016-2.940)	<0.00001
ECG findings (normal/pathological), n	27/21	44/13	0.007
Echocardiographic findings (normal/pathological), n	39/9	44/13	0.126
IVIG treatment (yes/no), n	24/24	14/43	0.012

Continuous variables are presented as median (min-max), and categorical variables as numerical values (n). Continuous variables were compared using the Mann-Whitney U test, and categorical variables using the chi-square test
IVIG: Intravenous immunoglobulin, ECG: Electrocardiography

examined the relationship between IVIG treatment and clinical course. The main findings of our study were that elevated troponin T levels were frequently observed in children with suspected myocarditis, pathological ECG findings—particularly ST-segment elevation—were associated with higher troponin levels, and IVIG therapy was more frequently administered in patients with CMR-CM. However, IVIG treatment was not associated with improvement in left ventricular systolic function or shortened time to troponin normalization.

Cardiac troponins are well-known biomarkers of myocardial injury and are widely used in the diagnosis of myocarditis. In pediatric patients, troponin elevation generally reflects myocardial inflammation or injury; however, based on literature data, the relationship between troponin levels and the clinical course or prognosis of the disease has not always been consistent[8]. In our study, elevated troponin levels were detected in all patients at presentation and were considered an important biomarker supporting the diagnosis of suspected myocarditis. Similarly, previous pediatric studies have reported frequent troponin elevations in children diagnosed with myocarditis or myopericarditis[12-14].

Generally non-specific ECG abnormalities are commonly observed in myocarditis. In our study, pathological ECG findings were detected in approximately one-third of the patients. The most frequent abnormality was ST-segment elevation, which was associated with higher troponin levels. This finding suggests that ST-segment variations may reflect more pronounced myocardial injury in pediatric myocarditis. Previous studies have also reported that ST-segment and T-wave abnormalities are common in pediatric myocarditis; however, the diagnostic specificity of these findings remains limited[15]. Although sinus tachycardia has been reported as the most common arrhythmia in myocarditis[16], only one patient in our cohort developed supraventricular tachycardia requiring intervention, and ventricular tachycardia was not observed in this patient.

IVIG therapy is frequently used in pediatric myocarditis despite the lack of definitive evidence regarding its efficacy. Proposed mechanisms of action include neutralization of viral pathogens, modulation of the immune response, and suppression of pro-inflammatory cytokines. However, studies evaluating the effectiveness of IVIG therapy in pediatric myocarditis have reported conflicting results. In a Cochrane review by Robinson et al.[10], IVIG therapy was not associated with a significant impact on mortality or survival in children[17]. Similarly, Mounts et al.[18] reported that mortality in pediatric fulminant myocarditis is observed at a higher rate than in adults and emphasized that the evidence supporting the benefit of IVIG therapy remains limited.

In our study, IVIG therapy was not associated with a significant improvement in left ventricular systolic function. In addition, the time to troponin normalization was relatively prolonged in patients receiving IVIG therapy. However, this finding may reflect the fact that IVIG is typically administered to patients with more severe clinical presentations rather than a direct effect of the therapy itself. In other words, this observation may represent a type of selection bias. Indeed, in our cohort IVIG therapy was preferentially administered to patients with more severe clinical features, including higher troponin levels, significant ECG abnormalities, or left ventricular systolic dysfunction.

Previous studies have reported varying results regarding the effectiveness of IVIG therapy. Hyun Jung Kim et al.[19] reported that IVIG therapy had no significant effect on ventricular function or survival in pediatric myocarditis. In contrast, Huang et al.[20] and Drucker et al.[21] reported that IVIG therapy might be associated with improvement in ventricular function and increased survival. These inconsistent findings indicate that there is still no clear consensus regarding the role of IVIG therapy in pediatric myocarditis.

One notable observation in our study was the emergence of different cardiomyopathies during long-term follow-up in some patients. In one patient with recurrent troponin elevations and a family history of cardiomyopathy, genetic analysis revealed a mutation in the *DSP* gene, and follow-up findings were consistent with arrhythmogenic right ventricular dysplasia. *DSP* gene mutations have previously been reported to present initially with myocarditis-like clinical episodes[22]. Similarly, one of our patients was diagnosed with restrictive cardiomyopathy during follow-up. In addition, recurrent troponin elevations in one patient were found to be associated with macrotroponin positivity. Although macrotroponin is most commonly reported in association with troponin I, it may rarely accompany troponin T as well[23].

Study Limitations

This study has several limitations. First, it was a retrospective single-center study. Furthermore, the diagnosis of myocarditis was not histopathologically confirmed; instead, its diagnosis was based on clinical findings, elevated cardiac troponin levels, and CMRI findings. Since endomyocardial biopsy was not routinely performed, diagnostic misclassification may be performed in some patients.

Only patients who underwent cardiac MRI were included in the study, which may have introduced selection bias and may limit the generalizability of the results. Although troponin levels were evaluated serially, a systematic analysis of their relationship with some clinical indicators of disease severity—such as intensive care unit admission, inotropic support, severe arrhythmias, or mortality—could not be performed.

Additionally, echocardiographic assessment was largely based on conventional parameters, and strain echocardiography as well as detailed diastolic function analyses were not performed in all patients. Finally, the number of patients in certain subgroups, particularly those with PM receiving IVIG therapy, was limited, which prevented conduction of multivariable analyses.

CONCLUSION

In conclusion, cTnT levels represent an important biomarker supporting the diagnosis of suspected pediatric myocarditis and may provide useful information during follow-up. However, in this study IVIG therapy was not associated with a clear-cut improvement in clinical course or left ventricular systolic function. Since IVIG treatment was preferentially administered to patients with more severe clinical presentations, the longer time to normalization of troponin levels observed in the IVIG group most likely reflects baseline disease severity rather than a treatment effect. Larger -scale prospective multicenter studies are required to more clearly determine the true impact of IVIG therapy in pediatric myocarditis.

Ethics

Ethics Committee Approval: The ethical approval was obtained from the University of Health Sciences Türkiye Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital Ethics Committee (decision no: 2025/14-12, date: 02.09.2025).

Informed Consent: This is a retrospective study.

Footnotes

Author Contributions

Surgical and Medical Practices: M.M.B., Concept: M.M.Y., Design: O.H., Data Collection or Processing: C.D., Y.İ.D., Analysis or Interpretation: M.M.B., S.G., Literature Search: G.V., O.H., Writing: M.M.B.

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Original Article

Evaluation of Myocardial Function in Children with Vasovagal Syncope Using Speckle-Tracking Echocardiography

Vazovagal Senkoplu Çocuklarda Miyokard Fonksiyonunun Speckle-Tracking Ekokardiyografi ile Değerlendirilmesi

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ABSTRACT

Objective: Syncope is a transient, sudden and reversible loss of consciousness caused by cerebral hypoperfusion. The most common type of childhood syncope is neurally mediated syncope, with more than 50% of cases suffer from vasovagal syncope (VVS). Although VVS is commonly seen during both childhood and adulthood, its underlying pathogenesis and prognosis are still unclear. We have aimed to evaluate both left ventricular (LV) and left atrial myocardial function in children with VVS using two-dimensional speckle-tracking echocardiography (2D-STE) during the non-syncopal period.

Method: The study population included patients under the age of 18 years diagnosed with VVS based on patient history and physical examination findings. Cases with structural heart disease, arrhythmia, or syncope due to metabolic or neurological causes were excluded. The control group consisted of healthy children without systemic diseases.

Results: A total of 36 children with VVS and 36 healthy controls were included. No significant differences were found between the groups regarding age, gender, body mass index, systolic/diastolic blood pressure and heart rate. Conventional echocardiographic measurements showed no differences between both groups in terms of LV volume, systolic and diastolic functions. However, LV global longitudinal and circumferential strain, left atrial peak strain values were lower in the VVS group. LV global longitudinal strain, circumferential strain, and left atrial strain were significantly associated with the presence of syncope.

Conclusion: The study demonstrated that myocardial performance parameters are affected in children with VVS. In addition to conventional echocardiography, evaluation of cardiac functions with 2D-STE imaging will provide important information for these patients.

Keywords: Neurally mediated syncope, vasovagal syncope, two-dimensional speckle-tracking echocardiography, atrial function, ventricular function

ÖZ

Amaç: Senkop, serebral hipoperfüzyon nedeni ile ortaya çıkan geçici, ani ve geri döndürülebilir bilinç kaybıdır. Çocukluk çağında senkopun en yaygın nedeni nöral iletişim aracılı senkop olup, olguların %50'sinden fazlası vazovagal senkop (VVS)'dir. VVS hem çocukluk hem de yetişkinlikte yaygın olarak görülse de altta yatan patogenez ve prognoz hâlâ belirsizdir. Çalışmamızda VVS'li çocuklarda hem sol ventrikül hem de sol atriyal miyokardiyal fonksiyonları senkop olmayan dönemde iki boyutlu speckle-tracking ekokardiyografi (2D-STE) kullanarak değerlendirmeyi amaçladık.

Yöntem: Çalışmamıza 18 yaş altı hastalar dahil edildi ve hasta öyküsü ile fiziksel muayeneye dayanarak VVS teşhisi kondu. Metabolik veya nörolojik nedenlere bağlı, senkop, yapısal kalp hastalığı, aritmi nedenli senkop gelişen olgular hariç tutuldu. Kontrol grubu, sistemik hastalığı olmayan sağlıklı çocuklardan oluşturuldu.

Bulgular: VVS tanılı 36 çocuk ve adölesan, 36 sağlıklı çocuk dahil edildi. Gruplar arasında yaş, cinsiyet, vücut kütle indeksi, sistolik/diyastolik kan basıncı ve kalp atış hızı açısından anlamlı farklar bulunmadı. Geleneksel ekokardiyografik ölçümler, sol ventrikül (LV) hacminde, sistolik ve diyastolik fonksiyonlarda herhangi bir fark göstermedi. Ancak, LV global longitudinal strain, circumferential strain ve sol atriyal strain değerleri VVS grubunda daha düşüktü. Ek olarak LV global longitudinal, circumferential strain ve sol atriyal strain değerleri, senkopun bağımsız öngörücüleri olarak bulundu.

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Sonuç: Çalışmamız, VVS'li çocuklarda miyokard performans parametrelerinin etkilendiğini göstermiştir. Geleneksel ekokardiyografiye ek olarak, 2D-STE görüntüleme ile kardiyak fonksiyonun değerlendirilmesi bu hastalar için klinik tanı aşamasında önemli bilgiler sağlayacaktır.

Anahtar kelimeler: Nöral aracılı senkop, vazovagal senkop, speckle-tracking ekokardiyografi, atriyal fonksiyon, ventriküler fonksiyon

INTRODUCTION

Syncope can be defined as transient, sudden, completely reversible loss of consciousness accompanying with a loss of posture due to cerebral hypoperfusion[1].

Neural-mediated syncope (NMS) or orthostatic intolerance is the leading underlying disorder of pediatric syncope, frequently involving vasovagal syncope (VVS), postural tachycardia syndrome (POTS) and situational syncope. VVS is one of the common hemodynamic type of neurally mediated syncope accounting for more than 50% of cases in childhood[2,3]. Although VVS is commonly seen in both childhood and adulthood, the underlying pathogenesis and prognosis are still unclear and relevant studies are still ongoing. Autonomic nervous dysfunction, reflex vasodilation, vasomotor dysfunction, and genetic factors are considered as potential pathogenic mechanisms for VVS[4]. Another pathophysiologic cause that has been investigated is related to the function of the cardiac chambers. Some evidence now suggests that changes in cardiac chamber volume and function may be a determinant factor in recurrent episodes of syncope. However, further studies are needed to elucidate the precise roles of heart chamber functions in its pathogenesis.

Nowadays, advanced echocardiographic modalities such as two-dimensional speckle-tracking echocardiography (2D-STE) have made it possible to qualitatively assess myocardial performance in real-time. Compared with other echocardiographic methods, 2D-STE is an angle-independent method capable of direct myocardial function evaluation during the cardiac cycle by measuring related deformation markers. The systematic use of these modalities could contribute to the evaluation of the atrial and ventricular performance leading to further insights into the mechanism of VVS.

In the literature, we have not encountered a study that investigated atrial and ventricular myocardial performance in combination and evaluated cardiac function in childhood with VVS. In this study, we aimed to evaluate both left ventricular (LV) and left atrial (LA) myocardial function in children with VVS using 2D-STE during non-syncopal period.

MATERIALS and METHODS

This retrospective cross-sectional study was conducted between January 2023 and December 2023 at the department of pediatric cardiology. Medical records of patients who met the inclusion criteria during the study period were reviewed. Patients under the age of 18 diagnosed with NMS syncope were included in our study. Medical history and physical examinations of the study participants were reviewed as the first step in the diagnosis of NMS syncope. Episodes of syncope and the presence of predisposing factors were questioned. Patients who experienced at least two syncopal episodes within the last year were included in the study. Predisposing factors were considered to be: prolonged standing or sudden changes in body position (rapid change of body position from supine or sitting or squatting to upright), exposure to emotional stress, pain or occurrence of syncope during medical procedures. Concomitant prodromal symptoms including dizziness, nausea, weakness, paleness, and sweating were questioned. After history taking and physical examination, other diseases in the differential diagnosis of syncope were investigated. Patients with structural heart disease, arrhythmia detected by electrocardiographic examination and 24-hour Holter monitoring received the diagnosis of cardiac syncope and excluded from the study. In addition, patients diagnosed with syncope due to neurologic and metabolic causes were also excluded from the study.

Active standing and active sitting test were applied to patients with a preliminary diagnosis of NMS[5]. Based on the results of these tests, patients diagnosed with POTS, and patients with situational syncope were not included in the study. The diagnosis of VVS was made after excluding all other causes of syncope.

The control group included healthy children who presented to the pediatric cardiology clinic with complaints of chest pain or heart murmur but without any systemic diseases.

Complete medical history taking and physical examination were performed for all study participants. The age, weight, height, systolic blood pressure, and diastolic blood pressure (DBP) measurements and body mass index (BMI) of the study participants were recorded. BMI were calculated as follows: body weight (kg) divided by square of height (m^2). All patients underwent comprehensive transthoracic echocardiographic examinations. The echocardiographic examinations (described below) and all relevant data were recorded on data collection forms.

The study was conducted in accordance with the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Participants, and approved by the Institutional Ethics Committee of Buca Seyfi Demirsoy Training and Research Hospital (decision no: 2023/183, date: 25.10.2023). Informed consent was obtained from all patients and their families.

Conventional Echocardiography

We performed echocardiographic study in all included children according to the current guidelines of the American Society of Echocardiography[6]. Echocardiographic assessments were performed by using simultaneous electrocardiographic recordings with the help of the Philips Affiniti 50C ultrasound system by using appropriate transducers.

Images were obtained from parasternal and apical windows using 2D, M-mode, and Doppler echocardiography. M-mode echocardiography in parasternal long and short axis views were used to assess left ventricular (LV) systolic functions: LV end-diastolic diameter and end-systolic diameter, left ventricle end-diastolic volume and end-systolic volume (LVESV), fractional shortening (FS) and ejection fraction values were measured.

To determine LV diastolic functions; the mitral inflow signal was evaluated in the apical four-chamber view. Doppler echocardiography was used to measure the early (E) and late (A) diastolic flow velocities of the mitral valve, which were used to calculate the E/A ratio.

From the apical four- and two-chamber views, the maximum LA volume (LAV) was calculated using the area-length method according to the guidelines of the American Society of Echocardiography[6] .The LAV index (LAVI) was calculated as LAV divided by body surface area.

Speckle-Tracking Echocardiography

The 2D-STE examinations were performed with study participants in both patient and control groups. Standard grey-scale 2D images were obtained and frame rate was adjusted to 60-90 frames/second and three to five consecutive cardiac cycles synchronized to a continuous electrocardiogram were recorded. Post-processing of the digitally stored image data was performed offline using QLAB software.

LV longitudinal strain peak S values were measured by using the apical 4,3,2 chamber images and followed by averaging the three chambers and the determination of the global longitudinal strain value. Circumferential strain was measured in the standard parasternal short-axis at the papillary muscle plane.

For the left atrium 2D-STE analysis, images from the apical four and two chamber views was obtained. In order to calculate the LA strain (LAS), the atrial endocardial border was outlined manually in the end-systolic frame and the epicardial surface was calculated automatically[7].

Statistical Analysis

All data were analysed using SPSS Statistics version 23.0 for Windows software. Frequency and percentile values were noted for categorical variables. The chi-square test was used for the comparison of categorical variables.

Normality tests were conducted, and then for comparative analyses between the syncopal and non-syncopal groups, the Student's t-test was used in cases of normal distribution, and the Mann-Whitney U test was employed in cases of non-normal distribution. If the continuous variables were normally distributed, they were expressed as mean ± SD and median values (min, max). P-value of <0.05 was considered statistically significant.

The predictive value of the variables for the occurrence of the study endpoints was assessed using regression analyses. Univariate logistic regression analysis was initially performed to evaluate the association between clinical, echocardiographic, and strain parameters and syncope. Variables with $p<0.05$ were subsequently entered into multivariate logistic regression models adjusted for age and sex. Receiver operating characteristic (ROC) curve analysis was subsequently performed to assess the discriminatory ability of significant echocardiographic and strain parameters for identifying patients with syncope. The optimal cut-off values were determined using the Youden index.

A post-hoc power analysis was performed for the primary comparison of LV global longitudinal strain between the syncope and control groups.

RESULTS

Thirty-six patients with VVS and 36 healthy children in the control group were included in the study. There were 10 male (27.8%) and 26 female (72.2%) patients in the syncope and 17 male (47.2%) and 19 female (52.8%) participants in the control group. There was no difference in age, sex, BMI, systolic and DBP parameters between syncope and control groups. There was no significant difference between heart rates during echocardiographic examination in the non-syncope period. The demographic characteristics and clinical features of the study population are presented in Table 1.

The conventional echocardiographic parameters, including LV end-diastolic, end-systolic diameters, LV end-diastolic volume, LVESV were not different between the study groups. LV systolic functions did not show any statistically significant difference between the patient and control groups in terms of EF, FS values.

In the evaluation of LV diastolic function, The E/A ratio was lower -though not statistically significant- in patients with VVS.

LAVI was 24.77±1.55 mL/m^2, 24.16±1.53 mL/m^2 in syncope and control group respectively. There was no difference in the measurement in both groups. The conventional echocardiographic findings are presented in Table 2.

LV strain parameters, including LV global longitudinal strain (-17.86±1.88 vs -19.49±2.22) and circumferential strain (-18.68±1.00 vs -21.25±2.28) were observed to be lower in the patient group compared to the control group. LA peak strain was observed to be lower in patients with syncope compared to the control group (35.67±4.18 vs 44.13±7.08). The 2D- STE data are presented in Table 3.

In the univariate logistic regression analysis, demographic, echocardiographic and clinical variables potentially associated with the presence of syncope were evaluated individually. Among these variables, LV longitudinal strain, LV circumferential strain, and LAS measurements were found to have statistically significant potential predictive value for the development of syncope. The results of the univariate regression analysis are presented in Table 4. Due to potential collinearity between strain parameters, each strain variable was tested in a separate logistic regression model adjusted for age and sex. In separate logistic regression models adjusted for age and sex, LV longitudinal strain, LV circumferential strain, LAS measurements were each significantly associated with the presence of syncope. The results of the multivariable logistic regression model are presented in Table 5. ROC curve analysis demonstrated that LV global longitudinal strain had a moderate ability to discriminate patients with syncope from controls [area under the curve (AUC)=0.73], cutoff value of -18.5%, predicted syncope with 72.2% sensitivity and 70% specificity and LA peak strain showed a higher discriminatory performance (AUC=0.85) cutoff value of 39.2%, predicted syncope with 77.8 % sensitivity and 80.6% specificity. Post-hoc power analysis for the primary comparison demonstrated a statistical power of 91%.

Table 1. Demographic characteristics and clinical features of the study population

Variables	Syncope group (n=36)	Control group (n=36)	p-value
Age (years)	13.33±3.16	12.41±3.45	0.24
Sex (male:female)	10:26	17:19	0.08
BMI (kg/m^2)	21.3±0.79	19.21±3.83	0.11
Heart rate (bpm)	74.5±10.8	78.58±11.35	0.12
SBP (mmhg)	110.77±9.46	110.41±15.60	0.67
DBP (mmhg)	71.66±6.21	70.27±6.54	0.28

BMI: Body mass index, DBP: Diastolic blood pressure, SBP: Systolic blood pressure

Table 2. Conventional echocardiographic findings of the study population

Variables	Syncope group	Control group	p-value
Ejection fraction (%)	72.86±2.93	73.25±3.67	0.62
Fractional shortening (%)	42.44±2.84	42.30±3.14	0.84
LVEDD (cm)	4.16±0.39	4.26±0.44	0.29
LVESD (cm)	2.35±0.19	2.46±0.31	0.06
LVEDV (mL)	68.69±3.56	69.36±3.51	0.42
LVESV (mL)	15.69±2.67	16.77±2.40	0.075
E-wave/A-wave	1.91±0.24	2.01±0.20	0.06
LAVI (mL/m^2)	24.77±1.55	24.16±1.53	0.09

LV: Left ventricular, EDD: End diastolic diameter, ESD: End systolic diameter, EDV: End-diastolic volume, ESV: End-systolic volume, E/A: Transmitral flow velocity ratio, LAVI: Left atrial volume index

Table 3. 2D-speckle tracking derived peak systolic LA and LV strain results					
Variables	Syncope group	Control group	Mean difference	95% CI	p-value
Left ventricle global longitudinal strain (%)	-17.86±1.88	-19.49±2.22	1.63	0.66-2.60	0.001*
Left ventricle circumferential strain (%)	-18.68±1.00	-21.25±2.28	2.56	1.72-3.40	0.001*
Left atrial peak systolic strain (%)	35.67±4.18	44.13±7.08	8.46	5.71-11.21	<0.001*

*p<0.05
CI: Confidence interval, LA: Left atrial LV: Left ventricular

Table 4. Univariate Regression Model results of echocardiographic parameters for the presence of syncope			
	Univariate analysis results		
	Statistics	OR (95% CI)	p-value
E-wave/A-wave	0.13	0.01-1.14	0.066
Left ventricle global longitudinal strain (%)	0.66	0.50-0.87	0.004
Left ventricle circumferential strain (%)	0.19	0.09-0.43	0.000
LAVI (mL/m^2)	1.3	0.95-1.78	0.102
Left atrial peak systolic strain (%)	0.75	0.66-0.86	0.000

Result variable: Presence of syncope. Exposure variables: Echocardiographic parameters
Adjust variables: None, LAVI: Left atrial volume index, CI: Confidence interval, OR: Odds ratio

Table 5. The relationship between strain parameters and syncope in different models					
LV global longitudinal strain		LV circumferential strain		Left atrial peak systolic strain	
Model 1		Model 2		Model 3	
OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95% CI)	p-value
0.64 (0.47-0.85)	0.003	0.18 (0.08-0.41)	0.000	0.76 (0.66-0.87)	0.000

Model 1, 2, 3 was adjusted for age and sex.
The Hosmer-Lemeshow test was used to assess the goodness of fit of the discriminant model. Hosmer-Lemeshow testi p>0.05.
OR: Odds ratio, LV: Left ventricular, CI: Confidence interval

DISCUSSION

Our study is the first to evaluate both LA and LV myocardial performance in patients with VVS in the pediatric age group. The relationship between cardiac chamber functions and syncope in these patients with syncope is not yet clear. Although there are different studies on this subject in both pediatric and adult patients, to our knowledge, there is no study in which both atrial and ventricular cardiac strain parameters were investigated using 2D-STE method in the pediatric age group.

The left atrium provides a critical relationship in ensuring LV performance through reservoir, conduit, and booster pump functions during the cardiac cycle. LAV measurements are strongly correlated with the assessment of cardiovascular diseases and the prediction of outcomes, but increasely accumulating data shows that the evaluation of LA functions provides more prognostic information(8-10). At this point, the evaluation of LA functions has gained increasing importance, especially with the growing use of 2D-STE, which has allowed for earlier assessment and recognition of changes in LA functions, because it provides more reliable and accurate measurements compared to other measurement methods(11,12). In a study evaluating LAV in adult patients with VVS, maximal and minimal LAV were found to be lower in VVS patients compared to the healthy control group(13). In another study in adults, it was reported that patients with VVS under 35 years of age had better atrial contractility than patients with VVS over 35 years of age, but both LA and right atrial volumes were lower. As a result, it has been argued that in patients with syncope at an early age, the reduction of preload is more prominent and the recurrence of syncope is more frequent(14). In our study, unlike them, both patients in the childhood age group were evaluated, and there was no significant difference in LAV measurements between patients with syncope and the healthy group. Başanalan et al.[15] measured the LA ejection force using the mitral valve orifice area and a wave as a reference and reported that in patients with VVS who were head-up tilt test (HUTT) positive, the force was lower compared to those who were HUTT negative. Additionally, when they evaluated LA phasic functions[10] with tissue Doppler imaging, they did not observe a difference between the two groups. However, their measurements are more angle-dependent measurements, while we directly measured LA deformation in our study. We found that in the measurement of LA deformation parameters during the non-syncopal period, patients with VVS had lower LA systolic functions compared to the control group.

It is accepted that increased sympathetic activity occurs with the increase of blood catecholamine (epinephrine and norepinephrine) levels in the initial stage of NMS. Younger patients with HUTT-positivity have been shown to have higher epinephrine release in the pre-syncope period compared to older patients. This result led to the conclusion that there are fluctuations in epinephrine/norepinephrine levels that change with age[16]. As a result of all this, it has been reported that the decrease in preload and the accompanying atrial functions are less effective in the etiology of syncope[17,18]. Our study was conducted during periods without syncope in children with syncope recurrence. It was observed that atrial contraction were fewer in patients at rest. Based on this result, we can say that due to the relatively fewer atrial contractions at baseline, patients are unable to provide sufficient systolic power at the onset of syncope.

Another possible reason playing a role in pathophysiology is the ventricular theory. According to the ventricular theory, it is thought that syncope occurs due to an increase in cardiac contractility caused by high catecholamine levels during syncope, resulting in activation of mechanoreceptors subsequent withdrawal of the sympathetic system and an increase in vagal tone[4,18]. It is still being investigated because, in some adult studies, the opposite results have been reported, and it has been argued that strong contraction of the LV is less responsible for the decrease in LV volume[19,20]. Liu et al.[21] reported a decrease in end- systolic stress, cardiac index, and LV end-diastolic volume predicting a positive tilt test.

The "ventricular theory" in patients with VVS was questioned by Goel et al.[22] in 2013 and reported that paradoxical reduction in LV strain was observed in patients with VVS and HUTT(+). Although the results seem to be contrary to the excessive contractility advocated in the ventricular theory, they reported that they obtained different results due to the fact that the evaluations were performed at rest and direct myocardial deformation was measured. Similarly, in our study, when we evaluated myocardial deformity in patients with VVS, we found that LV strain was lower. Similar results were reported by Hensel et al.[3] indicating that the LV resting longitudinal strain rate at rest in patients with VVS was lower than in the control group which was more pronounced during HUTT.

Additionally, in the present study, LV global longitudinal strain, circumferential strain, and LAS were significantly associated with syncope. These findings suggest that subclinical alterations in myocardial mechanics may be associated with syncope, even in the absence of overt structural cardiac abnormalities. ROC analysis showed that LV global longitudinal strain had a moderate discriminatory ability, whereas LA peak strain demonstrated a stronger ability to differentiate patients with syncope from controls.

Study Limitations

The primary limitation of our study is that it was conducted as a single-center study with a cross-sectional design and a limited sample size. Another limiting factor was that we were not able to perform the HUTT, which would have allowed us to determine the subtypes of VVS in patients initially diagnosed with neurally mediated syncope and evaluated as VVS. This was due to the unavailability of this test at our center. However, there are studies in the literature that recommend performing this test only in cases where differential diagnosis cannot be achieved through a typical clinical history and physical examination, given the challenges associated with its application[23,24]. Consistent with these findings, another study has indicated that the presence of syncope episodes in the clinical history is a strong predictor of HUTT positivity[25].

CONCLUSIONS

In this study, we observed that myocardial strain parameters were affected in patients with VVS in childhood compared to the healthy group. However, it is fair to say that it is not possible to explain the etiology with cardiac chamber function alone. In addition to conventional echocardiography, evaluation of cardiac functions with 2D-STE imaging will provide important information for these patients. However, given the relatively small sample size and the absence of longitudinal follow-up, these findings should be interpreted with caution. In the follow-up of patients with syncope in childhood is to reduce recurrences and improve quality of life. Further large-scale prospective studies are needed to clarify the potential diagnostic and prognostic role of 2D-STE in this patient population.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Participants, and approved by the Institutional Ethics Committee of Buca Seyfi Demirsoy Training and Research Hospital (decision no: 2023/183, date: 25.10.2023).

Informed Consent: This is a retrospective study.

Footnotes

Conflict of Interest: The author disclose no potential conflicts of interest.

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Case Report

Dental Anomalies in a Pediatric Patient with 16p13.11 Recurrent Microdeletion Syndrome: A Case Report

16p13.11 Rekürrent Mikrodelesyon Sendromlu Çocuk Hastada Dental Anomaliler: Olgu Sunumu

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ABSTRACT

Recurrent 16p13.11 microdeletion syndrome is a rare genetic condition with variable clinical manifestations. This report aims to highlight the craniofacial and dental features of a pediatric patient with this syndrome, emphasizing the importance of early dental evaluation in children with genetic disorders. A 7-year-old girl diagnosed with recurrent 16p13.11 microdeletion syndrome, who had no previous dental examination, was evaluated. Clinical and radiographic findings revealed microcephaly, retrognathic maxilla, Class III appearance, oligodontia, delayed tooth eruption, and malformations in crown and root morphology. Dental caries in molars were restored with glass ionomer, compomer, and composite resin. Due to mental retardation and poor cooperation of the patient, removable prosthetic rehabilitation was not planned. Oral hygiene education was provided, and follow-up visits were scheduled. This case underlines the significance of early dental assessment in patients with genetic syndromes and emphasizes the need for multidisciplinary management and long-term follow-up.

Keywords: Pediatric dentistry, syndrome, chromosome deletion, oral manifestations

ÖZ

Rekürrent 16p13.11 mikrodelesyon sendromu, değişken klinik özellikler gösterebilen nadir bir genetik durumdur. Bu olgu sunumunda, söz konusu sendroma sahip pediatrik bir hastanın kraniyofasiyal ve dental bulgularının vurgulanması ve genetik bozukluğu olan çocuklarda erken dental değerlendirmenin öneminin ortaya konması amaçlanmıştır. Daha önce hiç dental muayenesi yapılmamış, 16p13.11 rekürrent mikrodelesyon sendromu tanısı bulunan 7 yaşındaki bir kız hasta değerlendirilmiştir. Klinik ve radyografik incelemelerde mikrosefali, retrognatik maksilla, Sınıf III görünüm, oligodonti, gecikmiş diş sürmesi ve kuron-kök morfolojisinde bozukluklar gözlenmiştir. Molar dişlerdeki çürükler cam iyonomer, kompomer ve kompozit rezin ile restore edilmiştir. Zihinsel yetersizlik ve eksik kooperasyon nedeniyle hareketli protetik rehabilitasyon planlanmamıştır. Hastaya oral hijyen eğitimi verilmiş ve takip randevuları planlanmıştır. Bu olgu, genetik sendromu olan hastalarda erken dental değerlendirmenin önemini ortaya koymakta ve multidisipliner yaklaşım ile uzun dönemli takibin gerekliliğini vurgulamaktadır.

Anahtar kelimeler: Çocuk diş hekimliği, sendrom, kromozom delesyonu, oral bulgular

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INTRODUCTION

Genetic syndromes are complex disease groups that are frequently encountered in childhood, and often involve multiple organ systems[1]. They may develop due to chromosomal anomalies, monogenic disorders, or submicroscopic genomic alterations such as microdeletions and microduplications[1]. Although their clinical manifestations vary significantly among individuals, neurodevelopmental delay, musculoskeletal abnormalities, dysmorphic facial features, congenital heart defects, and orofacial malformations have been widely reported in pediatric patients[1,2]. Orofacial findings, in particular, may directly, and adversely affect feeding, speech, and psychosocial development, and may also provide important diagnostic clues[2]. Some genetic syndromes also have significant adverse effects on oral and dental health in childhood[2]. For example, individuals with Down syndrome are prone to develop macroglossia, a high-arched palate, delayed tooth eruption, and periodontal disease, while patients with ectodermal dysplasia commonly present with marked hypodontia, conical-shaped teeth, and enamel hypoplasia[3]. Treacher Collins syndrome may affect craniofacial development, causing cleft lip and palate, mandibular hypoplasia, and associated respiratory complications[3]. In Williams syndrome, wide diastemas, hypoplastic enamel structures, and malocclusions have been reported in addition to the characteristic "elfin" facies syndrome[4]. In most of these syndromes, dental abnormalities appear at early ages and often require long-term planning and multidisciplinary intervention[2].

The recurrent 16p13.11 microdeletion syndrome is a rare genetic syndrome with variable phenotypic features[5]. It is characterized by a 0.8-3.3 Mb deletion located on the short arm of chromosome 16 and involves genes such as *NDE1*, *NTAN1*, *MYH11*, *ABCC6*, *MPV17L*[5]. The *NDE1* gene plays a critical role in the development of cerebral cortex, and deletions involving this gene have been strongly associated with neurodevelopmental disorders, including microcephaly[5]. The *NTAN1* gene is thought to play a role in regulating synaptic activity and the formation of social behaviors[6].

The clinical phenotype of the syndrome may include a wide spectrum of symptoms such as global developmental delay, epilepsy, microcephaly, hypotonia, autism spectrum disorder, attention-deficit hyperactivity disorder, low birth weight, and behavioral disturbances[7,8]. Dysmorphic craniofacial manifestations such as low-set ears, a thin upper lip, a short nose, a wide mouth, micrognathia, and downward-sloping palpebral fissures have also been described[9]. These craniofacial manifestations indicate that orofacial structures are functionally affected, as several genes located within the 16p13.11 region play critical roles in the development of ectodermal-derived tissues[8,9]. Although uncommon, a broad spectrum of dental anomalies has been documented in patients with 16p13.11 microdeletion, including congenital tooth deficiencies (hypodontia and oligodontia), structural enamel defects, malocclusion, and delayed tooth eruption[8,10].

In this case report, we present a 7-year-old girl diagnosed with recurrent 16p13.11 microdeletion syndrome who had no previous dental examination. The aim is to describe the coexistence of oligodontia and multiple developmental dental anomalies, and to emphasize the importance of early multidisciplinary evaluation of patients with similar manifestations.

CASE REPORT

This observational clinical case study. Describes a pediatric patient diagnosed with recurrent 16p13.11 microdeletion syndrome. Because this is a single-patient report, no inclusion or exclusion criteria were applied. Clinical and radiographic examinations, including panoramic imaging, were performed, and medical history, dental findings, treatment planning, and follow-up records were reviewed to ensure diagnostic reliability.

A 7-year-old girl diagnosed with 16p13.11 recurrent microdeletion syndrome was admitted to the Ege University. Faculty of Dentistry, Department of Pedodontics, on February 20, 2025, with the complaint of multiple missing teeth and spontaneous exfoliation of existing teeth.

Review of the patient's medical history revealed that microarray analysis conducted at the Genetic Diseases Evaluation Center on 22 October, 2021 had detected a 1.25 Mb deletion within the 16p13.11 chromosomal region. This deletion involved seven *OMIM* genes including *NTAN1*, *RRN3*, *MARF1*, *MYH11*, *FOPNL*, *ABCC1*, and *ABCC6*. These manifestations were reported as a pathogenic variant consistent with recurrent 16p13.11 microdeletion syndrome. The deletion in the same chromosome region was also detected in the patient's father without any clinical or phenotypic abnormality, and genetic examination of the mother was unremarkable.

Family medical history did not reveal any problems related to the cardiovascular, neurologic, or urinary systems. Extraoral examination revealed developmental delay and a Class III facial appearance. Based on clinical findings and previous medical evaluations, the patient had received the diagnosis of intellectual disability.

Panoramic radiograph obtained on February 20, 2025, showed bilateral congenital absence of the upper and lower permanent lateral incisors, both of lower central

Figure 1. Panoramic radiograph at first admission showing oligodontia and crown-root malformations

permanent incisors, and upper right permanent second premolar (Figure 1). Excluding the third molars, seven permanent teeth were missing, leading to a diagnosis of oligodontia. Intraoral examination confirmed the absence of these teeth in both dental arches.

According to the parent's report, the anterior teeth in both jaws had previously exfoliated once, and based on this information, the upper right and left central incisors present at admission were interpreted as permanent teeth. Radiographic evaluation also revealed crown and root malformations in several developing permanent tooth germs (Figure 1). In addition, the crown dimensions of these teeth were smaller than normal, consistent with the diagnosis of microdontia (Figure 1). Significant variation was noted in the eruption paths of the tooth germs, and some showed deviation from the anatomical eruption line, with oblique angulation and rotational irregularities (Figure 1).

Intraoral and radiographic examinations demonstrated dentin caries in the upper right and left deciduous second molars, as well as fissure caries in the lower right and left first permanent molars (Figure 1). Increased dental mobility was noted in the maxillary central incisors which was evidenced radiographically by root resorption (Figure 1). Due to the patient's intellectual disability and limited cooperation, intraoral photographic documentation could not be completed during the first visit.

The carious lesion on the upper right deciduous second molar was cleaned with hand instruments, and a glass ionomer restoration was placed to improve patient comfort and relieve pain. The patient was recalled six months later for follow-up. During this visit, cooperation had improved; therefore, detailed extraoral and intraoral examinations could be performed, and intraoral photographs were obtained. Frontal and lateral photographs revealed a prominent Class III facial profile due to retrognathic maxilla and protrusive mandible (Figures 2a, and 2b). Mild microcephaly, a flat nasal bridge, downward-sloping palpebral fissures, a thin upper lip, and low-set ears were also observed (Figure 2a).

In the second intraoral examination, the permanent upper central incisors that had been present at the first visit were missing (Figure 3a). Considering the previously noted advanced mobility and radiographic root resorption, it was concluded that these teeth exfoliated spontaneously. All maxillary anterior incisors were absent. In the maxillary arch, deciduous second molars and permanent first molars were present bilaterally in the posterior region (Figure 3a). Moderate mobility and dentin caries were detected in the upper left deciduous second molar, and fissure caries were found on the permanent molars (Figure 3a).

In the mandibular arch, right and left permanent first molars were present, and fissure caries lesions were observed on their occlusal surfaces (Figure 3b). The right deciduous mandibular canine showed mobility with significant accumulation of dental calculus (tartar) and gingival inflammation (Figure 3b).

Due to the numerous missing teeth and delayed eruption, inadequate development of the dental arches

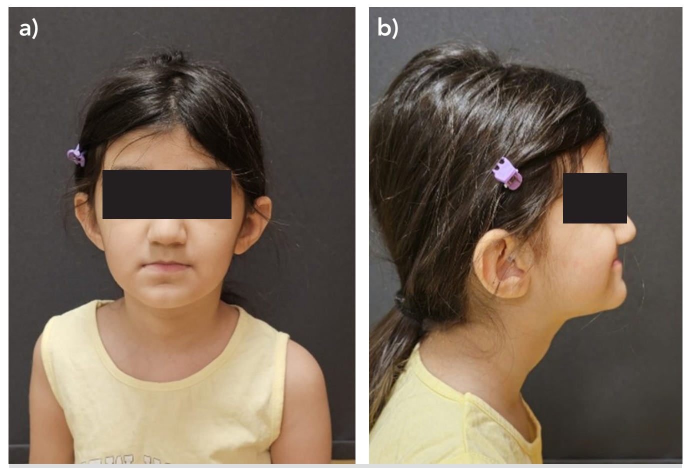

Figure 2. Extraoral views: (a) frontal view with microcephaly and dysmorphic features. (b) lateral view with retrognathic maxilla and class III profile

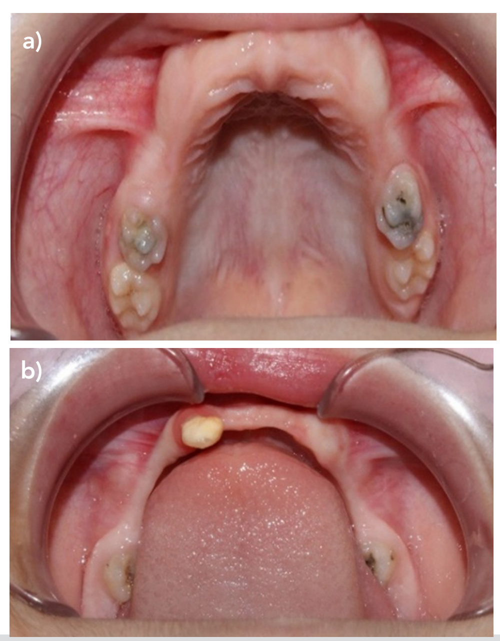

Figure 3. Intraoral occlusal views: (a) missing maxillary incisors and knife-edge alveolar crest. (b) mandible with calculus accumulation and gingival inflammation

was observed. A "knife-edge" alveolar crest was present in both the maxilla and mandible, characterized by narrow, high, and sharply contoured alveolar ridges (Figures 3a, and 3b).

The panoramic radiograph obtained during the second visit confirmed these findings. Radiographic examination revealed advanced resorption of the roots of the right deciduous mandibular canine and the left deciduous maxillary second molar, suggesting that spontaneous exfoliation could occur (Figure 4). Similar to the first radiograph, many permanent tooth germs were congenitally absent, and the existing germs were positioned at different angulations with developmental crown and root abnormalities (Figure 4). The crown and root structures demonstrated marked hypoplasia, and the roots were short and conical (Figure 4).

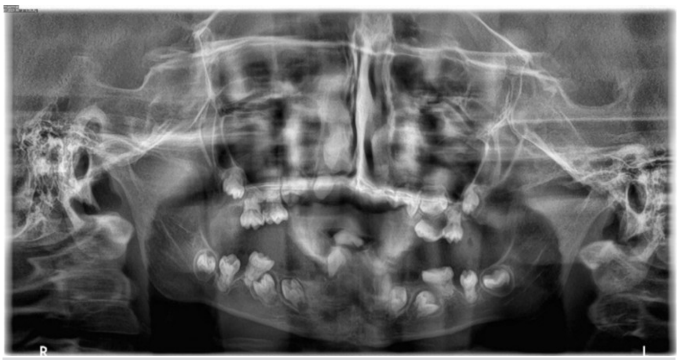

Figure 4. Follow-up panoramic radiograph showing abnormal eruption pathways and root hypoplasia

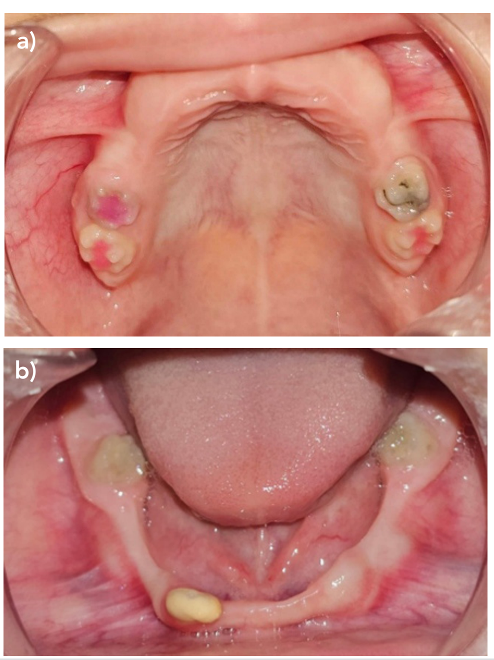

Figure 5. Post-treatment occlusal views: (a) maxilla after compomer restorations. (b) mandible after composite resin restorations

During subsequent treatment sessions, caries in the upper right and left permanent first molars and the upper right deciduous second molar were removed, and the teeth were restored with compomer (Figure 5a). Carious lesions on the permanent mandibular first molars were removed and restored with composite resin (Figure 5b). The upper left deciduous second molar and lower deciduous canine, both demonstrating moderate mobility, were retained under follow-up because the parents did not consent to extraction of these teeth (Figures 5a, and 5b).

Due to the patient's intellectual disability, limited ability to cooperate, and the presence of the narrow, high, and knife-edge shaped alveolar crests, removable prosthetic rehabilitation was not recommended under current conditions. Oral hygiene instructions were provided, and the patient was referred for regular follow-up visits.

DISCUSSION

The recurrent 16p13.11 microdeletion syndrome is a chromosomal disorder that may cause clinical diagnostic difficulties due to its rarity and the considerable variability in genotype-phenotype correlation[7,8]. Similar to the present case, phenotypically unaffected individuals carrying the same deletion have been reported, suggesting that variable expressivity and reduced penetrance may be influenced by environmental or epigenetic modifiers[7].

In the current patient, neurodevelopmental and craniofacial characteristics, including intellectual disability, microcephaly, retrognathic maxilla, and a prominent Class III skeletal profile were overlapped with the features previously described in the literature[8,9]. Dysmorphic facial traits such as a flat nasal bridge, downward-sloping palpebral fissures, a thin upper lip, and low-set ears were also consistent with this syndrome[9]. These clinical findings may assist clinicians in recognizing this syndrome and reinforces the indication for genetic testing in similar cases.

Only a limited number of studies have documented the orofacial manifestations of recurrent 16p13.11 microdeletion syndrome. Dental anomalies such as hypodontia or oligodontia, enamel defects, delayed eruption, and microdontia have been rarely reported in affected individuals[11,12]. In our patient, seven permanent teeth, excluding third molars, were congenitally absent, leading to a diagnosis of oligodontia. Therefore, this case contributes to the literature as a rare example of dental developmental anomalies associated with this chromosomal abnormality.

Radiographic examination clearly demonstrated malpositioned tooth germs, deviations in timing and direction of eruption, rotational anomalies, and developmental defects in crown and root morphology. These abnormalities can adversely affect quality of life not only functionally, but also esthetically and psychosocially. Furthermore, insufficient alveolar bone development due to multiple missing teeth resulted in narrow, high, pointed alveolar crests, which complicated dental prosthetic rehabilitation procedure.

Because of the patient's intellectual disability and behavioral problems, cooperation during dental treatment was limited. As a result, minimally invasive procedures were preferred, and removable prosthetic rehabilitation was postponed. Similar to our findings, previous studies have emphasized that lack of cooperation represents a significant challenge in the dental management of children with neurodevelopmental impairment[13].

In conclusion, this case provides a comprehensive example of the dental manifestations that may accompany 16p13.11 microdeletion syndrome. The coexistence of rarely reported findings, including oligodontia and developmental anomalies in dental morphology, supports the phenotypic diversity of this chromosomal disorder. These results underscore the need for a multidisciplinary approach in pediatric patients presenting with similar characteristics, as early diagnosis and intervention may contribute to improved functional, esthetic, and psychosocial outcomes.

Parents' Perspective

As parents, witnessing the impact of our child's dental condition on her quality of life was a difficult experience. After the completion of the initial treatments, her functional comfort improved, which provided reassurance and optimism for the future. We appreciate the clinical team for their care and remain hopeful about the upcoming prosthetic treatment.

Ethics

Informed Consent: Written informed consent was obtained from the patient's parents for publication of this case report and the accompanying clinical images.

Footnotes

Authorship Contributions

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

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