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Echogenicity and size of substantia nigra on transcranial sonography (TCS) in patients with attention-deficit/hyperactivity disorder and healthy children aged 6–12 years: a comparative study

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Abstract

Background: Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neuropsychiatric disorders. Children with ADHD may experience significant functional problems, such as academic concerns at school, poor interpersonal relationships and low self-esteem. Current models of ADHD suggest that it is associated with functional impairments in dopamine and norepinephrine systems. The substantia nigra in the midbrain produces the largest amount of dopamine in the brain. The present study was conducted using TCS to compare the size and echogenicity of substantia nigra between ADHD and healthy children.

Results: This cross-sectional, analytical study was conducted on 68 (34 ADHD and 34 healthy individuals) aged 6–12 years. Based on the results obtained, the hyper-echogenicity of SN in control and ADHD groups were 33.3% and 66.7% ($P < 0.001$) and hypo-echogenicity of thalamic nuclei were 55.2% and 44.8% ($P < 0.05$), respectively. Interestingly, the TCS results of healthy children with a positive family history of ADHD were similar to results for patients with the disorder.

Conclusions: The echogenicity of Substantia nigra and thalamus nucleus among children and adolescents with ADHD is significantly higher from that in healthy children.

Keywords: Attention-deficit/hyperactivity disorder, Substantia nigra, Transcranial sonography

Background

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neuropsychiatric disorders in pre-school children, adolescents, and even adults [1, 2]. The disease is inherited by about 75% and affects 5.3% of people across the world; comparatively, In Iran, the prevalence of this disorder is almost similar and is

approximately 4% [3]. Although genetics and environmental factors are influential in the occurrence of this disorder, the exact mechanism of their impact has not been revealed so far. The examination and diagnosis of ADHD depends primarily on clinical interviews, including pediatric medical and social history [4]. A pattern of permanent decrease in attention or increase in impulsivity and hyperactivity characterized the disease [1, 2].

Children with ADHD may experience significant function problems, such as academic concerns at school [5], poor interpersonal relationships with family and

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peers, and low self-esteem. This disorder is associated with psychosocial and psychoneurological disabilities [5, 6] and increased risk of suicide [7]. In addition, these children are likely to score lower on academic achievement tests than other children, indicating evidence of academic failure [8]. It has been shown that these children can develop antisocial behaviors, substance abuse, and mood disorders, despite relative improvement [8]. Therefore, both early diagnosis and treatment of ADHD may improve the development of these children in all aspects. Insufficient diagnostic skills will lead to unnecessary drug treatments, which will lead to therapeutic deviations; hence, these people will suffer from drug side effects and an increase in the cost of medical treatment imposed subsequently on the health system. Therefore, the use of a paraclinical method in diagnosing the etiology will help to reduce misdiagnosis and negative consequences. Contributing paraclinic in this regard is Transcranial sonography (TCS) that represents echogenicity (intensity of reflected sound waves) in different parenchymal regions of the brain [9].

The TCS is a non-invasive procedure that can expose any changes in echogenicity in the brain parenchyma. This method is also able to measure different dimensions of the brain and can be used in the diagnosis of neurodegenerative and psychological diseases [10, 11]. The increasing use of TCS in the diagnosis of neuropsychiatric disorders around the world can confirm the high value of this method [10].

Current models of ADHD suggest that it is associated with functional impairments in some of the brain's neurotransmitter systems, particularly those involving dopamine and norepinephrine [12, 13]. The dopamine and norepinephrine pathways that originate in the ventral tegmental area and locus coeruleus project to diverse regions of the brain and govern a variety of cognitive processes. The dopamine and norepinephrine pathways that project to the prefrontal cortex and striatum are directly responsible for modulating executive function (cognitive control of behavior), motivation, reward perception, and motor function. These pathways known to play a central role in the pathophysiology of ADHD [12, 14]. Additional pathway is suggested by larger models of ADHD. Based on the results of previous studies, one of the main pathophysiology of ADHD is a change in the metabolic level of dopamine. One of the pathways producing the most dopamine in the brain is substantia nigra in the midbrain, whose disorder can explain hyperactivity in children with ADHD [15, 16]. A study by Marcel Romans in 2009 through TCS proved that substantia nigra in ADHD patients is larger than the general population. In addition, all patients in this study were treated by medication [12].

Given the advantages of TCS, including ease of use, availability and no side effects, this study employed TCS to evaluate the size and echogenicity of substantia nigra in ADHD patients compared with healthy children.

Methods

The present cross-sectional, analytical study was conducted among the population of ADHD patients and healthy children in the age group of 6–12 years referred to Kargarnejad Hospital in Kashan (Iran) in 2020. Based on the study by Romanos and colleagues [12], the sample size was estimated to be 68 (including 34 in the healthy group and 34 in the ADHD group), which were selected by convenience sampling method. Inclusion criteria were newly diagnosed patients with definitive diagnosis of ADHD based on clinical interview of specialist and having a suitable temporal window for ultrasound. Exclusion criteria were a history of other psychiatric disorders, non-cooperation in performing ultrasound, the patient's IQ out of the normal range, a history of obvious neurological disorders, and receiving any medication (including stimulants).

Throughout the study, the ADHD patients with a definitive diagnosis underwent TCS by means of interviews and clinical signs based on DSM5 criteria. (Use of SonoSite Edge II ultrasound machine, FUJIFILM SonoSite, USA and 1–5 MHz Phased probe model rP19x, temporal window). TCS was performed by a neurologist with more than 10 years of transcranial ultrasound experience, who was unaware of the child diagnosis. Ultrasound and selection of the appropriate window to view the basal nuclei of the brain were performed by the neurologist as well. By the same time, another people from the research team commented on the difference in echogenicity in the nucleus and the images were saved for re-evaluation. In cases where their opinions were contradictory, the recorded images were observed by a sonographer (with radiology area of expertise) and if the patient's image was not clear for the observer, the patient was removed from the study group.

The consent of the children and their parents was obtained before the ultrasound. Play equipment was placed in the ultrasound room to calm the children. A child psychologist involved children in play. The children saw how the ultrasound was performed and their cooperation for the ultrasound was drawn, so that hyperactive children could not be identified from healthy children.

In the control group, healthy children selected among children and relatives of hospital staff underwent ultrasound if they were in perfect health following clinical interview and psychological examinations.

The SN echogenicity was compared to that of red nuclei (RN) at the same level (Fig. 1A, B). Isoechoic has

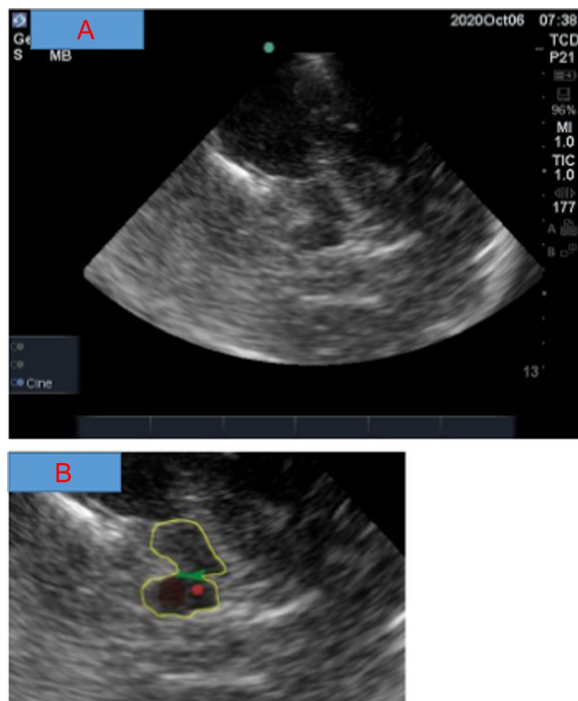


Fig. 1 Mid-brain and visible compartment. **A** Trans-temporal approach, midbrain plane. **B** Yellow line indicates the margin of the midbrain, red nucleus in red, Raphe nucleus in green and substantia nigra in brown

a similar echogenicity with RN, Hyperechoic when it has a higher density and hypoechoic when red nuclei are seen but the substantia nigra is not detectable (Fig. 2A–C) [17].

The echogenicity of the thalamus is normally lower than that of the surrounding tissues. In addition, it is easily recognizable due to its proximity to the third ventricle (Fig. 3A, B). Normally, these tissues are hypoechoic and considered isoechoic when the densities are similar to adjacent tissues (with lenticular nuclei) and hyperechoic when the density is similar to the occipital horn of the lateral ventricle (Fig. 4A, B) [17]. The lenticular nuclei are

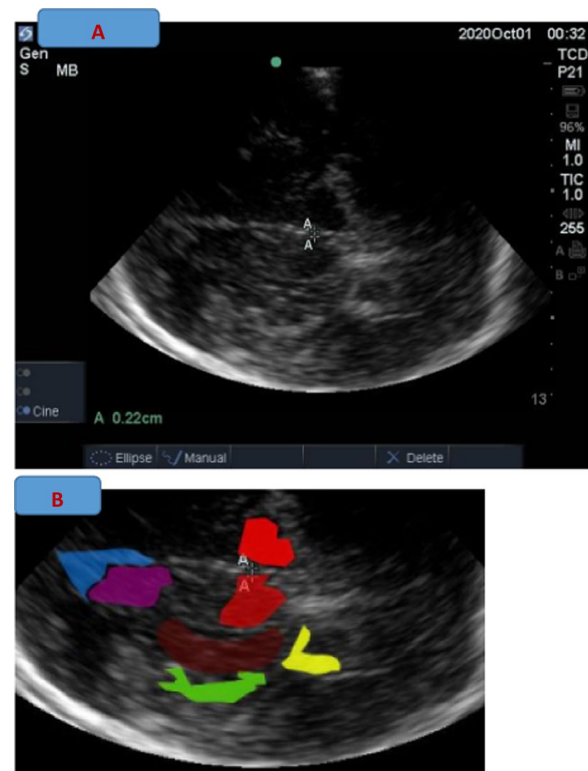


Fig. 3 Anatomy and location of 3rd Ventricle, Frontal and occipital horn, Thalamus, lentiform nucleus and Sylvian fissure. **A** Temporal window at the level of the thalamus. **B** + A was showed the walls of the third ventricle, bottom same image with the thalamus in red (usually hypo-echo and located on both sides of the third ventricle), anterior horn of the lateral ventricle in blue, dentate nucleus in purple, occipital horn of lateral ventricle in Yellow, Sylvian groove in green and lentiform nucleus in brown

located between the thalamus and the Sylvian fissure and are more echogenic than the thalamus and less than the Sylvian fissure or occipital horn (Fig. 3) [17].

For further evaluation, the image was saved from all sections in which the measurement was made. After sonography, patients' information was evaluated and compared by the researcher.

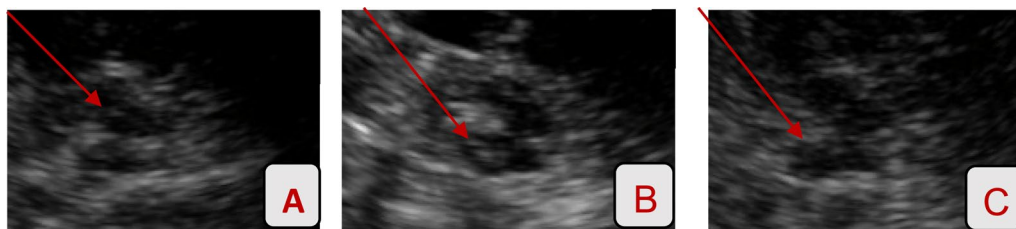


Fig. 2 Abnormal echogenicity of the SN. **A–C** show normal echogenicity, increasing echogenicity, and area decreasing echogenicity, respectively (Figure C shows only red nuclei in the medial)

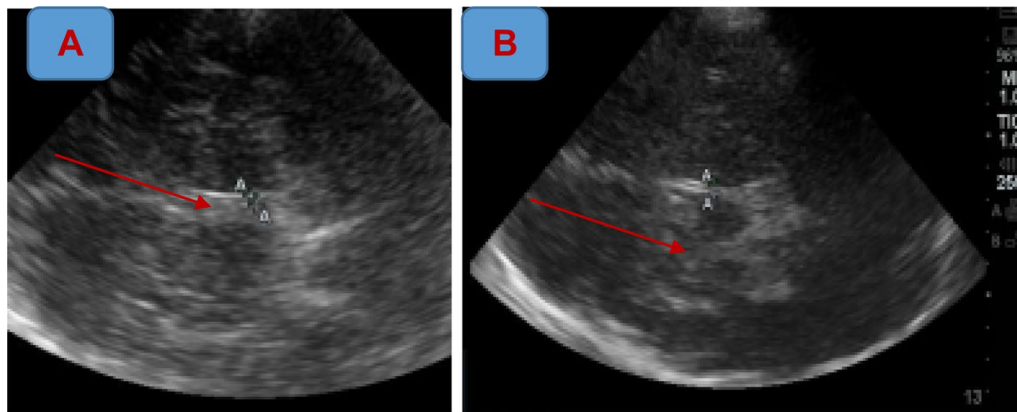


Fig. 4 Abnormal echogenicity of the thalamus and lentiform nucleus. **A** Increased echogenicity of the thalamus (compared to normal hypo-echo state and similar to occipital horn) (Arrow), **B** increased echogenicity of the lentiform nucleus (Arrow)

The findings, after collecting and correcting the bugs and outlier, were analyzed and described by measures of central tendency in terms of the type of distribution through tables and graphs. Comparisons between the two groups were performed using independent *t* test, and chi-square test for qualitative variables. Before main analysis, the confounder variables, including age, sex and order of birth, were compared in two study groups. In cases with significant difference, the confounder effects adjusted using linear regression in which the dependent variable was SN size and the independent one having ADHD disorder. SPSS17 software (developed by International Business Machines Corporation (IBM), 2008, USA) was employed for analysis. The significance level was less than 0.05. In this study, due to the qualitative nature of TCS data, which were expressed as hypoechoic, isoechoic and hyperechoic cases, significant relationship between qualitative data of echogenicity was compared by cross tab and chi-square test at 95% confidence interval (95%CI) and significance level of *p* value less than 0.05 ($P < 0.05$). Significance comparison of quantitative data was performed by independent *t* test.

Results

Patient enrollment in the study continued until 34 patients were completed in each group. (39 hyperactive children were included in the study of whom two refused to undergo ultrasound and three did not have a suitable window, and 37 healthy children were included in the study of whom one did not have a suitable window; so, the results regarding echogenicity were not confirmed, and two children refused to do the sonography). In both groups, 28 boys and 6 girls were equally selected. Based on descriptive analytical results, the mean age was 7.40 ± 1.70 and 9.03 ± 1.90 in ADHD and healthy groups,

Table 1 Frequency (percentage) of birth order and positive family history

Variables		Control	ADHD	<i>P</i> value
Birth order	First	14 (41.2)	12 (35.3)	0.091
	Second	14 (41.2)	15 (44.2)	
	Third and more	6 (17.6)	7 (20.6)	
Positive family history		15 (44.2)	26 (76.5)	0.021

respectively ($P = 0.001$). Other demographic information including birth order and positive family history is available in Table 1.

In this study, substantia nigra, echogenicity of thalamic nuclei, caudate nucleus, putamen nucleus and raphe nucleus were investigated; the results are reported in Table 2. Based on the results obtained from the echogenicity of substantia nigra, the frequencies of hyperechoic in control and ADHD groups were 33.3% and 66.7%, respectively ($P < 0.001$). For echogenicity of thalamic nuclei and hypoechoic category, the frequencies were 55.2% and 44.8% ($P < 0.05$). However, the findings from the echogenicity of caudate, putamen and raphe nuclei indicated that the two groups of ADHD and healthy did not differ significantly ($P > 0.05$). Other details are presented in Table 2.

In this study, in connection with measuring the size of substantia nigra, three values of A (right nucleus area), B (left nucleus area) and C (nucleus perimeter) were measured on both the right and left. Among the measurements of the right and left sides of each person in each part A, B and C, the highest value for the person was considered. Then, the two groups were compared using linear regression model while adjusting age. According

Table 2 Frequency (percentage) of echogenicity of different areas in patients participating in the study

Variables	Control			ADHD			P value
	Hypoecho	Isoecho	Hyperecho	Hypoecho	Isoecho	Hyperecho	
Echogenicity of substantia nigra nuclei	0 (0)	21 (72.4)	13 (33.3)	0 (0)	8 (27.6)	26 (66.7)	<0.001
Echogenicity of thalamic nuclei	32 (55.2)	2 (20)	0 (0)	26 (44.8)	8 (80)	0 (0)	0.04
Echogenicity of caudate nucleus	0 (0)	32 (51.6)	2 (33.3)	0 (0)	30 (44.8)	4 (66.7)	0.67
Echogenicity of putamen nucleus	0 (0)	32 (50)	2 (50)	0 (0)	32 (50)	2 (50)	1.00
Echogenicity of raphe nucleus	4 (66.7)	12 (48)	16 (45.7)	2 (33.4)	13 (52)	19 (54.3)	0.63

Table 3 Descriptive analysis of perimeter and area Substancia nigra nucleus in two groups; healthy and ADHD

SN nucleus	Control	ADHD
A (cm ²)	0.14 ± 0.81	0.18 ± 0.83
B (cm ²)	0.11 ± 0.34	0.15 ± 0.37
C (cm)	0.39 ± 2.21	0.43 ± 2.24

A: right nucleus area, B: left nucleus area, C: nucleus perimeter

SN: substantia nigra, ADHD: Attention-Deficit/Hyperactivity Disorder

Table 4 Comparison of perimeter and area substantia nigra nucleus in two groups, using linear regression model

Model		Unstandardized coefficients		Standardized coefficients	Sig.
		B	Std. Error		
A	Group	0.036	0.045	0.108	0.424
	Age	0.013	0.011	0.151	0.266
B	Group	0.046	0.036	0.173	0.200
	Age	0.009	0.009	0.139	0.302
C	Group	0.079	0.111	0.096	0.479
	Age	0.030	0.028	0.146	0.281

Sig. significance

For parameter estimating (beta) ordinary least square (OLS) method was used and for determining significance *t* test was applied

to the results, no significant differences were observed in any of the cases (Tables 3, 4).

In this study, the distance between the two walls of the third ventricle in the two groups was examined and compared. According to the results of this measurement, the mean length was calculated 0.32 ± 0.07 and 0.31 ± 0.07 in ADHD and healthy groups, respectively; there was no significant difference between the two groups based on the results of Mann–Whitney test ($P = 0.05$).

Discussion

Cranial ultrasound is a relatively new neuroimaging technique that shows tissue echogenicity (intensity of reflected ultrasound waves in the brain) through a

healthy skull, first identified by neurodegenerative disorders and psychiatry in many centers around the world that is probably the best evidence for the value of this method. A wider application of TCS is in early diagnosis, differential diagnosis and screening of ADHD children. Therefore, the current study aimed to evaluate and compare the size of substantia nigra and other basal nuclei on TCS in ADHD and healthy children.

The findings of this study showed that the echogenicity of substantia nigra and thalamic nuclei was higher in the ADHD children compared to the control group. There was no significant difference in the size and echogenicity of other brain nuclei between the control group and the ADHD children. According to the echogenicity findings of substantia nigra, the frequency of isoechoic cases was 27.6% and 72.4%, and the frequency of hyperechoic cases was 66.7% and 33.3% for both patient and healthy groups, respectively, showing a significant difference between the two groups. Based on the results obtained from the echogenicity of thalamic nuclei, the frequency of hypoechoic cases was 76.5% and 55.2% and the frequency of isoechoic cases was 23.5% and 6% in the patient and healthy groups, respectively, indicating a significant difference between the two groups.

Analysis on the family history of children revealed that the results of TCS for healthy children with a positive family history of ADHD are significantly similar to the results of TCS for patients with this disorder.

Limited knowledge is available about changes in the echogenicity of substantia nigra over a lifetime with age. On the other hand, the size of this nucleus does not change much with age, but the maturation of substantia nigra is delayed [18, 19], which can be in turn a factor in reducing its echogenicity slower and play a role in pathophysiology. However, previous studies have shown that the echogenicity of substantia nigra decreases with age in adults, and dopaminergic neurons are lost with age [20]. A study reported a gradual decrease in the echogenicity of substantia nigra in 109 children aged 0–192 months, indicating age-related changes occurring in the first decade of life [21]. However, no significant association

between the echogenicity of substantia nigra and the age of children was found.

The hypothesis that there is a delay in brain development in ADHD children compared to healthy children justifies the differences and sizes between different brain nuclei [22, 23]. Examining the studies to determine the difference in echogenicity of substantia nigra and thalamic nuclei by TCS, displayed that only one study used a method similar to the present study to examine echogenicity of brain nuclei in children with ADHD. However, there are many studies that have found such results with MRI. Daniella Berg in 2011 examined the intensity of substantia nigra using MRI and found that the intensity of substantia nigra is higher in ADHD children, in line with current findings that the nucleus echogenicity is higher in ADHD children than in the healthy group [24].

Weise (2009) found that ADHD patients had a larger substantia nigra area than healthy controls, indicating their dopamine dysfunction. This finding is similar to the results observed in Parkinson's disease [25]. Contrary to the studies, no significant difference in this regard was seen in the present study.

Bailey (2015) examined various brain components, and found abnormalities in the pulvinar region in ADHD patients; it is said that any part of the dopaminergic system, including the thalamus, can be disrupted by ADHD [26]. Findings about the difference in the echogenicity of thalamus between sick and healthy children are very limited, and this study, despite the small number of ADHD patients tested, cannot make a definite judgment about the echogenicity of thalamus in hyperactive patients. It is noteworthy that in the present study, by examining the echogenicity of thalamus in ADHD and healthy groups, the substantial finding was achieved that there is a significant difference in echogenicity between these two groups ($P=0.04$).

Drepper C introduced TCS as a new diagnostic method for determining changes in the echogenicity of subcortical brain structures in children with various disorders, such as obsessive-compulsive disorder, autism spectrum disorder, schizophrenia, panic disorder, ADHD, bipolar disorder and depression. However, the physical characteristics responsible for brain tissue echogenicity on TCS are principally unknown [10].

One of the limitations of this study was the method of selecting patients, which was performed qualitatively and not quantitatively. In addition, the accuracy of the findings depended on the quality of the ultrasound system as well as the competence of the researcher. Furthermore, due to the nature of the control sample, the control group did not fully represent the population from which the patient sample was taken.

Conclusions

Transcranial sonography is an easy and non-invasive method for assessing basal ganglia and substantia nigra nuclei of the brain. In general, it can be concluded from this study that the echogenicity of substantia nigra and thalamic nuclei in the group of children with attention-deficit/hyperactivity disorder are significantly different from the healthy group. It is also noteworthy that the study, which examined the family history of healthy children and the size of different brain nuclei, found that substantia nigra in children with a positive family history of hyperactivity significantly had substantia nigra tissue with larger echogenicity. This finding indicates the existence of a hereditary background in this disease and at the same time the presence of other factors essential for the occurrence of their disease.

Abbreviations

ADHD: Attention-deficit/hyperactivity disorder; TCS: Transcranial sonography; IQ: Intelligence quotient; DSM5: The diagnostic and statistical manual of mental disorders, fifth edition; MHz: Megahertz; RN: Red nucleus; SPSS: Statistical package for the social sciences; MRI: Magnetic resonance imaging.

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Author contributions

ZS, AA, RDK conceived the study, designed the experiments, and interpreted the results. ZS, FA supervised the study. ZS, FA, AA and SRmA carried out clinical assessment. RDK performed transcranial ultrasound. HR performed data analyses. AA, RDK wrote and edited the manuscript with support from ZS, FA and SRmA. All authors read and approved the final manuscript.

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Availability of data and materials

The raw data that support the conclusions of this article will be made available from the corresponding author after obtaining the permission of the Vice Chancellor for Research and Technology.

Declarations

Ethics approval and consent to participate

The study was conducted and approved by Dr. Smaeel Fakharian and Dr. Ahmad khorshidi (Director and Secretary of Instructional Research Ethics Committees. Faculty of Medicine and Faculty of Dentistry-Kashan University of Medical Sciences, respectively). Approval Date: 2020-12-09 and Approval ID: IR.KAUMS.MEDNT.REC.1399.163 available at: <https://ethics.research.ac.ir/PortalProposalList.php?code=IR.KAUMS.MEDNT.REC.1399.163>. The parents of the participants provided their written informed consent to participate in this study.

Consent for publication

The parents of the participants expressed their written consent to be published in this study without mentioning their personal details.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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