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Is there an association between cognitive impairment and urinary adrenaline, norepinephrine, gamma-aminobutyric acid, and taurine levels in children with obstructive sleep apnea?: A case control study

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Abstract

Background Children with obstructive sleep apnea (OSA) can develop cognitive impairments. Urinary adrenaline (EPI), norepinephrine (NE) and gamma-aminobutyric acid (GABA) are elevated, and taurine is decreased in children with OSA. The purpose of this study was to investigate the above-mentioned neurotransmitter levels in children with and without OSA, and explore their association with OSA-related cognitive impairments.

Methods Children underwent overnight polysomnography (PSG) for habitual snoring or mouth breathing in the pediatric sleep center from February 2023 to February 2024, as well as a group of healthy controls were enrolled in this study. Pediatric Quality of Life Inventory (PedsQL) and Child Behavior Checklist (CBCL) were used to evaluate the cognitive function of these children. Morning urine samples were collected to measure the urinary neurotransmitter levels.

Results This study recruited 74 children with OSA, 30 children with primary snoring (PS) and 16 healthy controls. In the comparison of PedsQL scores, social function (85(75, 100)), school function (65.88 ± 18.52), and total scores (74.15 ± 12.74) of OSA group were significantly lower than that of non-OSA group ($P < 0.05$); OSA group also exhibited increased withdrawn (1 (0, 2)) and attention problems (2 (1, 5)) scores in CBCL than non-OSA group ($P < 0.05$). A total of 39 cases in the OSA group (PedsQL total score below 77.42) were considered to have mild cognitive impairment (MCI), who had higher urinary EPI (190.68 ± 38.77 ng/ml) and lower taurine (432.20 ± 53.52 ng/ml) levels than both PS and OSA without MCI groups ($P < 0.001$). Logistic regression analysis showed that high levels of urinary NE ($OR = 1.027$, 95%CI: 1.002 ~ 1.052) and low levels of taurine ($OR = 0.982$, 95%CI: 0.969 ~ 0.995) are significantly associated with cognitive impairment in children with OSA, and their combination has a larger area under the curve (0.695) for prediction, with a sensitivity of 64.1% and specificity of 68.6% ($P = 0.004$).

Conclusions Children with OSA presented impaired cognitive functions such as school, social function deficits and attention problems. Measuring urinary EPI and taurine levels may contribute to the prediction of OSA-related cognitive impairments.

Keywords Obstructive sleep apnea, Cognitive impairment, Neurotransmitters, Children

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Background

Obstructive sleep apnea (OSA) is a breathing disorder during sleep, which is characterized by sleep fragmentation (SF) and intermittent hypoxia (IH). Typical clinical features of childhood OSA include snoring, frequent arousals and mouth breathing during nocturnal sleep, with obesity, tonsillar and/or adenoid hypertrophy as common risk factors [1, 2]. In addition, OSA can cause damage to multiple systems throughout the body, such as neurocognitive function, endocrine metabolism, renal and cardiovascular systems [3–5]. Untreated childhood OSA can progress to impairments of neurocognitive function [6, 7], which has arisen widespread concerns among parents. Preschool-aged children typically present with hyperactivity and inattention, while school-aged children often exhibit excessive daytime sleepiness, poor academic performance, and emotional instability [8].

The mechanisms of cognitive impairment associated with OSA are still under investigation, including blood flow/structural changes in the brain, increased oxidative stress, neuroinflammation and neuronal cell apoptosis [9–12]. For instance, recurrent hypoxia and reoxygenation triggered by IH can stimulate endothelial cells to produce reactive oxygen species (ROS), thereby promoting oxidative stress and neuro system dysfunction [7]. SF is another important feature of OSA, which can induce neuroinflammation and astrocyte activation, causing damage to the permeability of the blood–brain barrier (BBB) and apoptosis of neurons [13].

Currently, we can use polysomnography (PSG) accurately diagnose children with OSA [14]. However, few techniques are available for assessing cognitive impairment potentially caused by OSA in the early stages; therefore, exploring objective and convenient biomarkers to assess OSA-related cognitive impairment has become a research focus, including urinary neurotransmitters, serological indicators, magnetic resonance imaging (MRI) of the brain structures, and electroencephalogram (EEG) changes [15].

Hypoxia, abnormal gas exchange and frequent arousals caused by OSA can lead to continuous enhancement of sympathetic nerve activity [16], and this autonomic imbalance can cause abnormal changes of catecholamine levels in urine, manifesting as increased adrenaline (EPI) and norepinephrine (NE) levels [17–19]. With regard to changes in urinary neurotransmitter levels in children with OSA and cognitive impairment, the available evidence is insufficient. Kheirandish-Gozal et al. revealed that compared to control subjects, children with OSA exhibit elevated urine gamma-aminobutyric acid (GABA) and decreased taurine levels during nocturnal sleep, which may be the potential mechanism of neuronal excitotoxicity and dysfunction, and measuring their overnight changes can potentially predict the presence of cognitive impairment in children with OSA [20]. Gozal D et al. reported that children with OSA and neurocognitive deficits have significantly higher urinary 8-OH-dG levels than children with OSA alone [21], the predictive value of which for cognitive deficits in OSA group is not analyzed in their study. Thus, how urinary neurotransmitter levels change in children with OSA, with or without cognitive impairment, remains controversial, and further research appears warranted.

In this study, we analyzed the correlation between urinary EPI, NE, GABA, and taurine levels and cognitive impairment, in order to explore objective urine biomarkers for predicting cognitive impairment potentially caused by OSA.

Materials and methods

Participants

Individuals with snoring or mouth breathing during nocturnal sleep were recruited from the sleep center of the Department of Respiratory Medicine, Children's Hospital of Soochow University between February 2023 and February 2024. A total of 120 children were included in this study: 16 were healthy controls, 30 were diagnosed with primary snoring (PS) and 74 were diagnosed with OSA.

The inclusion criteria were as follows:1) children aged 3–12 years who could cooperate with overnight PSG recording for at least 8 h; 2) the children could empty their bladder before going to bed and had no habit of urinating at night; and 3) there was no vigorous exercise, intake of beverages or drugs on the day of PSG recording. The exclusion criteria were as follows:1) children who had undergone OSA-related therapy such as adenoidectomy and tonsillectomy, or have received treatment with oral orthopedic devices; 2) children who had other sleep disorders such as central sleep apnea and narcolepsy; 3) children who were in the acute or chronic phase of respiratory tract infections; and 4) children who had other diseases that can cause nocturnal hypoxemia such as nasal/facial deformities, cardiovascular diseases, hematological diseases, and neuromuscular diseases. This study was approved by the Medical Ethics Committee of the Children's Hospital of Soochow University (approval number: 2023CS058).

OSA diagnosis and assessment of cognitive function

The obstructive apnea hypopnea index (OAHI) was used to diagnose children with OSA and classify them into different severity groups; the PS group had an OAHI of <1 events/h. Mild OSA included children with an OAHI ≥ 1 but <5 events/h, and moderate/severe OSA included children with an OAHI >5 events/h.

Cognitive function was assessed using the Chinese versions of the Pediatric Quality of Life Inventory (PedsQL) and Child Behavior Checklist (CBCL). PedsQL is a commonly used tool for evaluating the quality of life in children, consisting of 23 items divided into 4 domains. The physical functioning domain included eight items, whereas the emotional, social, and school functioning domains each contained five items. Each item had five response options (0 = never, 1 = almost never, 2 = sometimes, 3 = often, and 4 = always), which were converted into a 100-point scale. The score for each domain was calculated by summing the scores of the items in that domain and dividing them by the number of items answered in that domain. The total score is the sum of the scores of all items divided by the total number of items answered in the entire questionnaire. In a study validating the Chinese version of PedsQL4.0 Children's Quality of Life Assessment Scale, the Cronbach's α coefficients for all four dimensions of the PedsQL4.0 exceed 0.7, indicating good reliability [22].

Additionally, we used the CBCL to evaluate the emotional and behavioral problems of the participants. The Chinese version of the CBCL/4–18 has been widely used to assess behavioral problems in children and has been proven to have good reliability and validity in studies on the autism spectrum and sleep disorders [23, 24]. CBCL/4–18 is classified into the following subscales: withdrawn, somatic complaints, anxious/depressed, social problems, thought problems, attention problems, delinquent behavior, and aggressive behavior. In the present study, those with a total PedsQL score below average were classified as mild cognitive impairment.

Hypoxic degree and obesity grouping

All patients were categorized based on the lowest pulse blood oxygen saturation ($LSpO_2$) at night into normal (≥92%), mild hypoxia (84%-91%), and moderate/severe hypoxia (≤84%) groups. According to the "Body mass index growth curves for Chinese children and adolescents aged 0 to 18 years", Body mass index (BMI) higher than or equal to the corresponding gender and age group's "overweight" threshold but less than the "obesity" threshold was considered overweight, while BMI higher than or equal to the corresponding gender and age group's "obesity" threshold is considered obese [25]. All others are defined as having a normal BMI.

PSG recording

Overnight PSG recording was performed using the Compumedics Grael and Philips Respironics Alice6 record system to diagnose OSA. It began at 8–9 p.m. and ended at 6–7 a.m. the following day. Major electrical activities such as right and left electrooculogram (EOG), EEG, submental electromyogram (EMG), and electrocardiogram (ECG) were recorded during the night. Meanwhile, sleep parameters such as oxygen desaturation index (ODI), time spent under 90% oxygen saturation (T90), $LSpO_2$, and OAHI were recorded and analyzed by experienced technicians at the sleep center.

Collection and analysis of urine samples

Morning urine samples were collected into a 5 mL urine specimen tube the next morning and stored in a -80 ℃ freezer until it was sent for testing. The concentrations of these neurotransmitters in the urine were tested using enzyme-linked immunosorbent assay (ELISA) at the Shanghai Saiyanbo Rui Biotechnology Company.

Statistical analysis

All data were analyzed using SPSS 27.0 and GraphPad Prism 8. Count data are expressed as the number of cases (%), and comparisons were conducted using the chi-square test. Quantitative data conforming to a normal distribution are expressed as mean ± standard deviation. Independent-sample *t* tests were used to compare two groups of variables, and one-way analysis of variance (ANOVA) was applied for comparisons involving two or more groups of variables followed by post hoc tests for pair-wise comparisons (LSD-least significant difference test). Non-normally distributed data are represented as [M (P25, P75)]. Comparisons between two groups of variables were performed using the Mann–Whitney U test, and the Kruskal–Wallis H test was used for comparisons involving two or more groups of variables followed by post hoc pair-wise tests after adjusting the significance level (Bonferroni correction). The associations between cognitive questionnaire scores and ODI, T90, and OAHI were analyzed using Spearman's rank correlation analysis. Logistic regression analysis was conducted to determine independent influencing factors of cognitive impairments in children with OSA, and receiver operating characteristic curves (ROC) were constructed to evaluate the diagnostic performance of urinary EPI and taurine. *P*-values < 0.05 were considered statistically significant.

Results

Demographic, PSG Characteristics and cognitive questionnaire scores

Demographic, PSG data and PedsQL and CBCL scores are shown in Table 1. A total of 120 cases were recruited in this study, including 16 healthy controls, 30 PS and 74 OSA children. There were no significant age or sex differences between the three groups, with significant differences in $LSpO_2$, OAHI, T90, and ODI between the

Table 1 Demographic, PSG data, and PedsQL and CBCL scores in controls, OSA, and PS groups

	Controls ($n=16$)	PS ($n=30$)	OSA($n=74$)	*P*
Sex (male/female, n)	10/6	17/13	45/29	0.904
Age (year)	7.65 ± 2.93	7.14 ± 2.18	7.48 ± 2.74	0.777
BMI (kg/m^2)	16.09 (14.86, 17.30) [a]	15.75 (14.53, 16.52) [b]	17.21(15.65, 20.50)	0.002**
OAHI (times/h)	N/A	0.45 (0.2, 0.7)[b]	4.1 (2.3, 8.22)	< 0.001***
$LSP0_2$ (%)	N/A	90 (88, 92)[d]	87 (81, 91)	< 0.001***
ODI (times/h)	N/A	0.20(0.08, 0.70)[b]	1.80 (0.38, 4.75)	< 0.001***
T90(min)	N/A	0.10 (0, 0.30)[b]	0.30 (0, 1.33)	0.040*
Total PedsQLscore	83.76 ± 7.78[c]	81.06 ± 12.01[d]	74.15 ± 12.74	0.003**
Body function	90.63(82.03, 96.88) [c]	85.94 (71.88, 93.75)	81.25 (65.63, 90.63)	0.006**
Emotion function	76.25 ± 14.78[c]	72.67 ± 15.16	66.96 ± 17.65	0.072
Social function	95(85, 100) [c]	100(75, 100)[d]	85(75, 100)	0.013*
School function	79.69 ± 13.35[c]	76 ± 16.63[d]	65.88 ± 18.52	0.002**
Total CBCL score	7.5(4, 11.25) [a,e]	21.5(10.25, 30.5)	22(11.5, 32)	< 0.001***
Withdrawn	0(0, 1)	0(0, 1) [b]	1(0, 2)	0.065
Somatic complaints	1(0, 1.75)	1(0, 2.25)	1(0, 2)	0.926
Anxious/depressed	1.5(0, 3.75) [a,e]	5.5(1, 5.5)	5(0, 5)	0.002**
Internalizing	3(0.5, 5.75) [a,e]	8(3.75, 12)	7(3, 14)	0.012*
Social problems	0.5(0, 2)	1(0, 3)	2(0, 3)	0.295
Thought problems	0(0, 1.75)	1(0, 1.25)	1(0, 2)	0.572
Attention problems	0(0, 1) [a,e]	1(0, 3) [b]	2(1, 5)	< 0.001***
Delinquent behavior	1(0, 1) [a,e]	2(1, 6)	2(1, 5)	0.009**
Aggressive behavior	1(0, 2) [a,e]	4(1, 6)	4(1, 7.5)	0.003**
Externalizing	2(1, 2.75) [a,e]	7(1, 11.25)	7(2.5, 12)	0.002**

PS primary snoring; *OSA* obstructive sleep apnea; *BMI* body mass index; *OAHI* obstructive apnea hypopnea index; *$LSpO_2$* lowest pulse blood oxygen saturation; *ODI* oxygen desaturation index; *T90* time spent under 90% oxygen saturation

[a] Control < OSA

[b] PS < OSA

[c] Control > OSA

[d] PS > OSA

[e] Control < PS

* $P<0.05$

** $P<0.01$

*** $P<0.001$

OSA and PS groups. OSA group had higher BMI than the other two groups(all $P<0.05$).

OSA group showed significantly lower school, social function and total scores in PedsQL (all $P<0.01$) compared with the other two groups. Among the OSA group, 32 cases had school function impairment, and 34 cases had social function impairment (below the corresponding average score).

With regard to the CBCL scale, withdrawn ($P=0.034$) and attention problems ($P=0.030$) scores were higher in the OSA group than in the PS group, and lower anxious/depressed, internalizing, attention problems, delinquent behavior, aggressive behavior, externalizing and total scores were observed in the control group compared with the other two groups (all $P<0.05$). Among the OSA group, 34 cases had attention problems, and 41 cases had withdrawn problems (above the corresponding median score).

Correlation analysis between ODI, T90, OAHI and cognitive questionnaire scores

The results of the Spearman correlation analysis between ODI, T90, OAHI and cognitive questionnaire scores are shown in Table 2 and Fig. 1. Body function ($r_s=$-0.252, $P=0.015$) and total PedsQL scores ($r_s=$-0.239, $P=0.022$) were negatively correlated with ODI, while somatic complaints, thought and attention problems scores were positively correlated with ODI ($r_s=0.206$, $P=0.048$; $r_s=0.215$, $P=0.040$; $r_s=0.217$, $P=0.038$, respectively). It also revealed that T90 have a good relationship between body

Table 2 Spearman correlation analysis between ODI, T90, OAHI and cognitive questionnaire scores

	ODI	T90	OAHI
	r_s *P*	r_s *P*	r_s *P*
Total PedsQLscore	-0.239 0.022*	-0.285 0.006**	-0.173 0.078
Body function	-0.252 0.015*	-0.230 0.027*	-0.104 0.292
Emotion function	-0.161 0.125	-0.156 0.137	-0.091 0.125
Social function	-0.185 0.077	-0.272 0.009**	-0.220 0.025*
School function	-0.187 0.074	-0.249 0.017*	-0.208 0.034*
Total CBCL score	0.190 0.070	0.075 0.474	0.012 0.901
Withdrawn	0.055 0.604	0.081 0.441	0.166 0.092
Somatic complaints	0.206 0.048*	0.143 0.175	-0.044 0.660
Anxious/depressed	0.119 0.259	0.067 0.527	-0.118 0.232
Internalizing	0.149 0.155	0.144 0.280	-0.074 0.457
Social problems	0.035 0.742	-0.025 0.810	-0.001 0.991
Thought problems	0.215 0.040*	0.238 0.022*	-0.091 0.357
Attention problems	0.217 0.038*	0.133 0.207	0.146 0.140
Delinquent behavior	0.073 0.488	-0.026 0.809	0.042 0.672
Aggressive behavior	0.060 0.570	-0.048 0.651	0.100 0.312
Externalizing	0.061 0.564	-0.050 0.638	0.079 0.424

ODI Oxygen desaturation index, *OAHI* obstructive apnea hypopnea index, *T90* time spent under 90% oxygen saturation

* $P<0.05$

** $P<0.01$

function, social function, school function and total PedsQL scores ($r_s=-0.230$, $P=0.027$; $r_s=-0.272$, $P=0.009$; $r_s=-0.249$, $P=0.017$; $r_s=-0.285$, $P=0.006$, respectively). OAHI was negatively correlated with school ($r_s=-0.208$, $P=0.034$) and social function ($r_s=-0.220$, $P=0.025$).

Urinary neurotransmitter levels between children with OSA and PS

Urinary neurotransmitter levels between PS, mild OSA, and moderate/severe OSA (MS OSA) groups are shown in Table 3. OSA group, including 47 mild OSA and 27 MS OSA, had higher EPI, NE and GABA and lower Taurine levels than PS group ($P<0.001$; $P<0.001$; $P<0.001$; $P=0.003$, respectively); Besides, MS OSA group had significantly higher levels of urinary NE than both PS and mild OSA groups.

Furthermore, A total of 39 cases (52.70%) of children with OSA (PedsQL total score below 77.42) were assessed as having mild cognitive impairment (MCI), who had higher EPI and lower taurine levels(all $P<0.05$) than both PS and OSA without MCI groups (Table 4).

Logistic regression analysis model for cognitive impairment in children with OSA

Logistic regression analysis model for cognitive impairment in children with OSA was performed, using the presence or absence of cognitive impairment as the dependent variable (0 = absent, 1 = present) and introducing sex (boy = 0, girl = 1), degree of hypoxia (0 = normal, 1 = mild hypoxia, 2 = moderate-to-severe hypoxia), and BMI level (0 = non-obese, 1 = overweight, 2 = obese), as categorical independent variables. Age, ODI, T90, urinary EPI, NE, GABA, and taurine levels were introduced as continuous independent variables. Urinary EPI (*OR* = 1.027, 95%*CI*: 1.002 ~ 1.052) and taurine (*OR* = 0.982, 95%*CI*: 0.969 ~ 0.995) levels were influencing factors for cognitive impairment in children with OSA. Children with obesity (*OR* = 14.278, 95%*CI*: 1.514 ~ 134.661) and moderate/severe hypoxia (*OR* = 7.975, 95%*CI*: 1.106 ~ 57.521) were more likely to exhibit cognitive impairment than children who had a normal BMI and $LSPO_2$ (Table 5).

Receiver operating characteristic of urinary taurine and EPI levels in OSA

Additionally, receiver operating characteristic curves were drawn for both urinary EPI and taurine levels, and then used in combination to predict OSA with MCI (Table 6). When the cutoff value of EPI was 205.15 ng/mL, the area under the curve (AUC) was 0.648, and it could predict cognitive impairment with a sensitivity of 48.7% and specificity of 77.1% ($P=0.028$). When the cutoff value of taurine was 436.8 ng/mL, the AUC was 0.666, and it could predict cognitive impairment with a sensitivity of 59.0% and specificity of 71.4% ($P=0.014$). The combination had a comparatively larger AUC (0.695), with a relatively higher sensitivity of 64.1% (Table 6 and Fig. 2).

Discussion

OSA can cause multi-dimensional damage to neurocognitive functions in children and that poor attention, memory, and executive ability are considered the main manifestations of cognitive impairments [26]. In our study, a total of 39 cases in OSA group were assessed as having mild cognitive impairment, presenting as school and social function decline, withdrawn, and attention problems. Children with OSA are prone to concentration difficulties, irritability and hyperactivity, and can progress to Attention Deficit Hyperactivity Disorder (ADHD) in severe cases [6, 27]. Wu et al. conducted a survey in 437 children with OSA (aged 4–11 years) and found that the proportion of ADHD was approximately 30% [28]. We found nearly half of the children with OSA (34 cases) have attention deficit problems in our research, and most of them are accompanied by impaired school functions (32 cases). Our assessment of school functions included items on memory and attention, and we thought that inattention and hyperactivity are closely linked to their poor school performance; In addition, memory impairments are one of the initial symptoms in

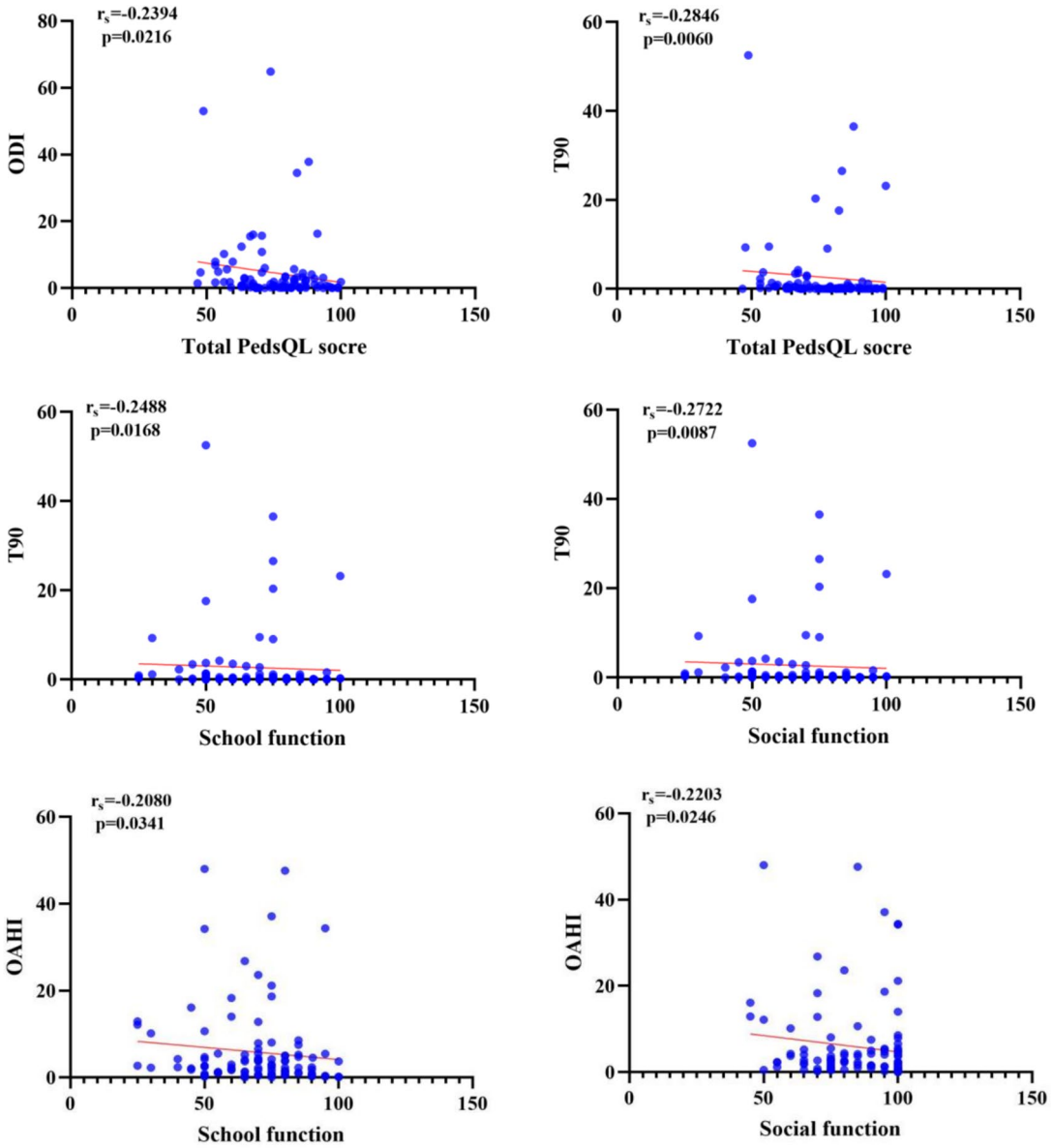

Fig. 1 Correlation between ODI, T90, OAHI and PedsQL scores

children with OSA, with short-term memory being the most severe, which may adversely affect their learning potential and neurocognitive development [29]. Fu-Jun Zhao et al. found that children with OSA have certain defects in facial emotion recognition, which may affect their social communication ability [30]. In our study, the assessment of social function also included aspects such as emotion expression, recognition and comprehension abilities, and it showed that a considerable number of children with OSA have social function impairment (34 cases) and withdrawn problems (41 cases). This may be attributed to the decline in emotion expression, facial expression recognition and comprehension abilities in these children, causing them to be easily alienated by other children.

As the age increases, the efficiency of OSA therapy may diminish, and the cognition impairment caused by OSA may become irreversible. A study by Song et al. found that preschool children with OSA have a significant improvement in cognitive function and IQ after pediatric adenotonsillectomy, whereas for older children, the benefits from treatments may be reduced [31]. Thus, early identification and intervention of OSA and its associated cognitive impairment is of great importance.

Table 3 Urinary neurotransmitter levels in the PS, mild OSA, and moderate/severe OSA groups

	PS ($n=30$)	Mild OSA ($n=47$)	MS OSA ($n=27$)	*P*
EPI (ng/mL)	122.10 ± 36.58[a,c]	185.44 ± 43.24	174.09 ± 39.88	< 0.001***
NE (pmol/L)	3 581.68 ± 225.90[a]	3 804.83 ± 615.87[b]	4284.49 ± 874.42	< 0.001***
GABA (μmol/L)	6.88 ± 1.13[a,c]	8.37 ± 0.78	7.90 ± 1.19	< 0.001***
Taurine (ng/mL)	507.65 ± 90.90[d,e]	450.21 ± 66.74	455.19 ± 65.00	0.003**

PS primary snoring, *OSA* obstructive sleep apnea, *MS OSA* moderate/severe OSA, *EPI* epinephrine, *NE* norepinephrine, *GABA* gamma-aminobutyric acid

[a] PS < MS OSA

[b] Mild OSA < MS OSA

[c] PS < Mild OSA

[d] PS > Mild OSA

[e] PS > MS OSA

** $P < 0.01$

*** $P < 0.001$

Table 4 Urinary transmitter levels in the PS, OSA without cognitive impairment, and OSA with cognitive impairment groups

	PS ($n=30$)	OSA without MCI ($n=35$)	OSA with MCI ($n=39$)	*P*
EPI (ng/mL)	122.10 ± 36.58[a,c]	170.84 ± 43.78[b]	190.68 ± 38.77	< 0.001***
NE (pmol/L)	3581.68 ± 225.90[a,c]	3915.42 ± 554.28	4037.66 ± 896.66	0.015*
GABA (μmol/L)	6.88 ± 1.13[a,c]	8.28 ± 0.96	8.36 ± 0.94	< 0.001***
Taurine (ng/mL)	507.65 ± 90.90[d,e]	474.12 ± 71.53[f]	432.21 ± 53.52	< 0.001***

PS primary snoring, *OSA* obstructive sleep apnea, *OSA without MCI* OSA without mild cognitive impairment, *OSA with MCI* OSA with mild cognitive impairment, *EPI* epinephrine, *NE* norepinephrine, *GABA* gamma-aminobutyric acid

[a] PS < OSA with MCI

[b] OSA without MCI < OSA with MCI

[c] PS < OSA without MCI

[d] PS > OSA without MCI

[e] PS > OSA with MCI

[f] OSA without MCI > OSA with MCI

* $P < 0.05$

*** $P < 0.001$

In the present study, we compared the urinary transmitter levels between OSA and PS children. There were no cases of nocturnal enuresis in the PS group and only 4 (5.41%) enuresis cases among the OSA group. Therefore, we believe that the enuresis has little effect on the results of urinary neurotransmitters in our study. In agreement with previous findings [17–19], we found elevated urine EPI and NE levels in OSA children. We noticed that in the MS OSA group, where there is severer IH and sleep fragmentation, urinary EPI levels are lower than those in mild OSA group. IH has been proved to result in continuous activation of the sympathetic nervous system [16, 32], which affects the output levels of catecholamines. IH also has differential effects on catecholamine release. In the short term, IH leads to an immediate and transient increase in plasma EPI levels, while NE concentrations rise with a delay and remain elevated after prolonged exposure to hypoxia [33, 34]. In the MS OSA group, NE levels were significantly higher compared to mild OSA groups, while there is no significant difference in EPI levels [17, 18], which is consistent with the findings of our study. Thus, we speculate that urinary NE levels may be more suitable for assessing the severity of OSA.

Urinary GABA levels were also significantly elevated in the OSA group. GABA is an important neurotransmitter involved in the regulation of sleep and wakefulness, and dysfunction of GABAergic pathways is one of the underlying mechanisms of OSA [35]. Increased GABAergic neural activity is associated with the severity of OSA [36], and the exacerbation of OSA often leads to hypoxia during sleep, causing excessive excitation of the prefrontal cortex and eventually resulting in neuronal dysfunction and cognitive impairment [8]. Kheirandish-Gozal et al. [20] showed that children with OSA and cognitive impairment indeed have a more significant increase in morning urinary GABA levels, whereas our study showed no significant differences in urinary GABA levels in OSA groups with different

Table 5 Logistic regression analysis model for cognitive impairment in the OSA group

		β	*S*	*Wald*	*P*	*OR*(95%*CI*)
Age		0.124	0.137	0.817	0.366	1.132 (0.865 ~ 1.481)
Sex						
Girl	Boy	1.007	0.732	1.895	0.169	2.738 (0.653 ~ 11.487)
BMI level				5.393	0.067	
Overweight	BMI normal	0.043	0.796	0.003	0.956	1.044 (0.220 ~ 4.969)
Obese		2.659	1.145	5.393	0.020*	14.278 (1.514 ~ 134.661)
Degree of hypoxia				4.465	0.107	
Mild Hypoxia	$LSPO_2$ normal	0.289	0.767	0.142	0.706	1.335 (0.297 ~ 6.000)
Moderate/severe hypoxia		2.076	1.008	4.242	0.039*	7.975 (1.106 ~ 57.521)
ODI		0.085	0.086	0.959	0.328	1.088 (0.919 ~ 1.289)
T90		0.192	0.087	3.545	0.060	0.825 (0.676 ~ 1.008)
EPI		0.027	0.012	4.542	0.033*	1.027(1.002 ~ 1.052)
NE		0.000	0.000	0.938	0.333	1.000(1.000 ~ 1.001)
GABA		-0.986	0.522	3.563	0.059	0.373(0.134 ~ 1.038)
Taurine		-0.018	0.007	6.912	0.009**	0.982(0.969 ~ 0.995)
Constant		7.442	4.627	2.587	0.108	

BMI Body mass index, *LSpO*$_2$ Lowest pulse blood oxygen saturation, *ODI* Oxygen desaturation index, *T90* time spent under 90% oxygen saturation, *EPI* epinephrine, *NE* Norepinephrine, *GABA* gamma-aminobutyric acid

* $P < 0.05$

** $P < 0.01$

Table 6 Value of urinary taurine, EPI, and their combination in predicting cognitive impairment in the OSA group

	AUC	cut-off value	*P*	95% CI	Sensitivity	Specificity
EPI (ng/mL)	0.648	205.15	0.028	0.524–0.773	0.487	0.771
Taurine (ng/mL)	0.666	436.8	0.014	0.543–0.789	0.590	0.714
Combination	0.695	0.576	0.004	0.576–0.814	0.641	0.686

EPI epinephrine, *AUC* area under the curve

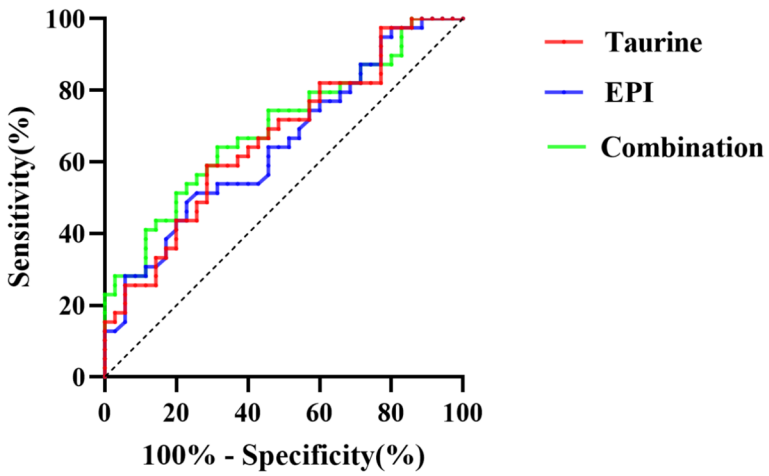

Fig. 2 Diagnostic performance of EPI, taurine and their combination. Area under the curve (AUC) of EPI = 0.648(95%*CI*: 0.524–0.773), *P* = 0.028; AUC of taurine = 0.666(95%*CI*: 0.543–0.789), *P* = 0.014; AUC of combination = 0.695(95% CI:0.576–0.814), *P* = 0.004

severity and with or without MCI. This result may be attributable to the relatively small number of MS OSA cases in our study, and multi-center studies and large sample of patients are needed in future. In addition, our study found that hypoxia-related indexes such as the ODI and T90, are significantly correlated with cognitive questionnaire scores, suggesting a close association between hypoxia and cognitive impairment.

Furthermore, we found that cognitive function measured by PedsQL scores is associated with urinary taurine and EPI levels, whereas children with OSA and cognitive impairment showed increased urinary EPI levels, which corresponded with the increased sympathetic activities caused by OSA-related hypoxia and sleep fragmentation [16]. In a study comparing wet nights and dry nights in children with nocturnal enuresis, there was a significant increase in metabolites and proteins associated with oxidative stress, and the levels of EPI were found to be 2.4 times higher on wet nights [37], suggesting close relationship between increased levels of urinary EPI and an increase in oxidative stress in the body. IH related to OSA triggers the production of reactive oxygen species, leading to an increase in oxidative stress in the body, which is closely associated with cognitive function impairment [7]. Given the close correlation between urinary EPI levels and oxidative stress in the body, this provides a plausible explanation for the increased levels of urinary EPI observed in children with MCI in our study. Nevertheless, as only few studies have reported the correlations between increased urinary EPI levels and cognitive impairment in OSA children, this result should be interpreted with caution.

In contrast, levels of taurine in the urine of children with cognitive impairment were significantly reduced. Taurine exerts neuroprotective effects by promoting the proliferation of brain cells and protecting them from damage caused by toxic mediators [38]. A decrease in urinary taurine levels was negatively correlated with the occurrence of cognitive impairment [39], suggesting that urinary taurine has a significant value in reflecting and assessing cognitive impairment. Kheirandish-Gozal et al. [20] found that urinary taurine levels in children with cognitive impairment significantly decreased throughout the night, which is consistent with our finding.

This study has several limitations. First, we conducted a cross-sectional study, and thus continuous and dynamic follow-up data of these children is needed to assess changes in their cognitive function for further analysis. Second, the assessment of cognitive function was relatively singular and susceptible to subjective influences, which may bias the results. Third, we only collected morning urine samples in this study. Urinary neurotransmitter levels may exhibit temporal variability; thus, multiple measurements and analyses across different periods should be performed in future studies.

Conclusions

In this study, children with OSA had abnormal levels of urinary neurotransmitters, characterized by increased levels of EPI, NE, and GABA, as well as decreased levels of taurine. The level of urinary NE positively correlated with the severity of OSA. Moreover, children with OSA were more prone to cognitive impairments, as evidenced by more school, social, and attention deficits in PedSQL and CBCL. Hypoxia and obesity were risk factors of cognitive impairment in children with OSA. Measuring urinary NE and taurine levels may help to distinguish cognitive impairment in children with OSA.

Abbreviations

ADHD	Attention deficit hyperactivity disorder
BBB	Blood-brain barrier
BMI	Body mass index
CBCL	Child Behavior Checklist
EEG	Electroencephalogram
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
EMG	Electromyogram
EOG	Electrooculogram
EPI	Adrenaline
GABA	Gamma-aminobutyric acid
IH	Intermittent hypoxia
$LSpO_2$	Lowest pulse blood oxygen saturation
MCI	Mild cognitive impairment
MRI	Magnetic resonance imaging
NE	Norepinephrine
OAHI	Obstructive apnea hypopnea index
ODI	Oxygen desaturation index
OSA	Obstructive sleep apnea
PedsQL	Pediatric Quality of Life Inventory
PS	Primary snoring
PSG	Polysomnography
ROS	Reactive oxygen species
SF	Sleep fragmentation
T90	Time spent under 90% oxygen saturation

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Authors' contributions

Jiapeng Ji completed statistical analysis and wrote the manuscript. Jiapeng Ji and Bolin Chen designed the research and participated in the collection of data. Xueyun Xu and Meng Lv interpreted the PSG Report. Yuqing Wang is the corresponding author of this article. All authors have reviewed and agreed to the published version of the manuscript.

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Data availability

The datasets used and/or analyzed during the current study are not publicly available due to ongoing research projects but are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Medical Ethics Committee of the Children's Hospital of Soochow University (approval number: 2023CS058). We confirm that informed consent was obtained from all subjects and/or their legal guardian(s).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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