CLINICAL ANALYSIS OF OBSTRUCTIVE SLEEP APNEA WITH HYPOPNEA COMBINED WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER

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ABSTRACT

Introduction*: A comparative study of dopamine/norepinephrine in children with pure obstructive sleep apnea hypopnea syndrome (OSAHS) and children OSAHS plus Attention deficit hyperactivity disorder (ADHD).*

Materials and methods: *A total of 437 children hospitalized for OSAHS from January 2014 to December 2014 were included in this trial. Based on the presence of ADHD and the ADHD classification, the patients were divided into a pure OSAHS group and a OSAHS plus ADHD group. The differences in the patients' gender, age, OSA-18 scores, sleep monitoring findings (AHI, lowest oxygen saturation), and serum dopamine and norepinephrine levels between the two groups were examined. SPSS20.0 was used for the statistical analysis.*

Results: *Men are more likely to suffer from OSAHS than women, and males are the majority of the children with ADHD in the present study. More serious respiratory events occurred among the children with OSAHS plus ADHD than among the pure OSAHS patients (P<0.001), and oxygen deficiency and sleep disorders were also more serious among the former group (P<0.01). The children with attention deficit-type ADHD and mixed-type ADHD had the worse sleep quality (P<0.001), and the OSA-18 scores were more severe among the children with ADHD plus sleep disorders (P<0.001). Among subjects aged 4-5 years, higher dopamine and dopamine/norepinephrine levels were observed among the children with ADHD (P<0.001). Children with hyperactivity-type ADHD had the highest levels, those with mixed-type ADHD had the second-highest levels, and those with pure OSAHS had the lowest levels. Norepinephrine levels were not significantly different between groups. In the 6 to 11-year-old group, the differences in dopamine, norepinephrine, and dopamine/norepinephrine levels were statistically significant (P<0.05), but dopamine and dopamine/norepinephrine levels were lower in the pure OSAHS group than in the group with OSAHS combined with hyperactivity-type ADHD.*

Conclusion: *The incidence of ADHD in children with OSAHS is more than 30%, which increases with age since longer durations of OSAHS have a more severe influence on the brain. Sleep disorders are more severe among children with OSAHS plus ADHD. Dopamine/norepinephrine levels are higher in children with hyperkinetic-type ADHD, suggesting that an imbalance between dopamine and norepinephrine is associated with hyperkinetic ADHD.*

Keywords: *Attention deficit hyperactivity disorder, obstructive sleep apnea hypopnea syndrome, dopamine, norepinephrine, comparative study, sleep disorders.*

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Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders in children. Its main presentations are attention disorders, restlessness, irritability, and impulsiveness. Children suffering from this disease are characterized by a lack of attention in performance. It is associated with hyperthyroidism and often co-occurs with learning difficulties, conduct disorder, tic disorders and certain emotional obstacles. ADHD can lead to poor performance, poor adaptation, low self-esteem, family stress and other problems in children. Failure to take timely intervention measures may lead to anti-social personality disorder or illegal and criminal behaviors, which will cause great harm to the children themselves and to society. Obstructive sleep apnea hypopnea syn-

drome (OSAHS) is characterized by the frequent recurrence of partial or complete airway obstruction during sleep. OSAHS disrupts normal ventilation and sleep structure and causes a series of pathophysiological changes. Children with OSAHS experience cognitive and executive function impairment and mood disorders.

Daytime sleepiness, low oxygen intake at night and disordered sleep perpetuate one another and aggravate the resulting damage, which leaves children more susceptible to the development of ADHD. The current literature indicates that OSAHS and ADHD in children are closely related. In this study, we aimed to investigate whether certain characteristics of OSAHS in children cause ADHD.

Objectives and methods

Objectives

From January 2014 to December 2014 at our hospital, PSG examination was used to identify OSAHS in children.

Children with schizophrenia, affective disorders, autism, epilepsy, liver degeneration, rheumatoid chorea, hyperthyroidism and other organic diseases were excluded. Respondents were excluded from the study if they were taking psychiatric drugs or if the child's guardian had difficulty completing the questionnaire due to low educational level. The study involved 441 patients.

Four of them were 12 years old and older, these four patients were eliminated because the number was too small to be analyzed. So the study included 437 children aged 4-11 years, including 298 males and 139 females, with a median age of 5 years.

Methods

Diagnostic methods and standards for OSAHS in children

OSAHS was diagnosed according to the Chinese Guideline for the Diagnosis and Treatment of OSAHS (Urumqi, Xinjiang, China)[1]. Obstructive sleep apnea (OSA) is defined by the persistent nasal/oral airflow obstruction for a specific duration (≥2 respiratory cycles) accompanied by chest and/or abdominal movement during dyspnea.

In the hypopnea sleep, the airflow intensity reduces to <50% with reduction in SaO2 by 0.03 and/or awakening. OSAHS is diagnosed if obstructive apnea index is above 1/h or AHI is above 5/h and the lowest SaO2 is less than 92%.

Diagnostic methods and criteria for ADHD in children

ADHD was diagnosed according to the DSM-IV[2] and 2011 Expert Consensus on the ADHD in Children[3]. After simple training, the children's guardians completed the evaluations according to the table, and the children were diagnosed with ADHD by the ADHD specialist.

There are 3 main subtypes of ADHD:

• Attention deficit: at least 6 out of 9 symptoms of attention deficit are met;

• Hyperactivity-impulsiveness: at least 6 of the 9 symptoms of hyperactivity and impulsiveness are met;

• Mixed type: simultaneously meeting at least 6 diagnostic criteria for the attention deficit and at least 6 criteria for hyperactivity-inattention.

The indicators are quantified as follows:

• The average score for all 18 items is the intention-hyperactivity score (IHS);

• The score for the first 9 items of the scale reflects attention deficit;

• And the score for the last 9 items reflects hyperactivity-impulsiveness.

PSG

The United States Polysmith36 Guided Sleep System (4.0) was used to monitor the children's nighttime sleep for at least 7 hours. The child was required to not have had any respiratory infections within 2 weeks of the monitoring and not to have taken sleeping pills, alcohol, tea or coffee in the 24 hours before the monitoring.

For the younger children, parents were permitted to stay in the monitoring room, peeing before sleep and not to engage in activity.

Quality of life score[4]

The OSA-18 scale includes five dimensions: sleep disorder, physical symptoms, bad mood, daytime functional status, and the impact on the child's relationship with caregivers. Each dimension comprises three or four items. According to frequency, the items are scored on a 7-point scale: 1=never, 2=almost never, 3=rarely, 4=sometimes, 5=often, 6=most of the time, and 7=always.

The higher the score, the worse the impact of sleep apnea on quality of life. Each child's score was calculated separately. The general scale score (ranging from 18 to 126) was used to evaluate the severity

of the effect of adenoid hypertrophy on the child's quality of life: <60 is mild, 60-80 is moderate, and >80 is severe. The scores of the various dimensions were used to evaluate the influence of adenoid hypertrophy on various aspects of quality of life.

The following variables were determined for all children diagnosed with OSAHS

Sex, age, height, weight, ADHD scale score, OSA-18 scale score, AHI index, minimum oxygen saturation during PSG examination, and serum dopamine and norepinephrine.

Statistical method

SPSS 24.0 was used for statistical analysis. The likelihood test was applied for qualitative data analysis. The four groups were compared using descriptive and comparative analyses.

Depending on whether the data were normally distributed, quantitative data are shown as mean (standard deviation) or median (range) based on analysis of variance and Kruskal Wallis H test, followed by the LSD method and Dunn or Dunn-Bonferroni post hoc analysis. Inspection level was set at α=0.05.

Results

The DSM-IV[2] is used as ADHD diagnostic criteria for children over 6 years of age, while in 2011, the ADHD expert consensus[3] lowered the age at diagnosis to 4 years, indicating the importance of early diagnosis of ADHD for therapeutic interventions and harm prevention. It is necessary to determine whether there are differences between children with ADHD under 6 years and those over 6 years; however, there are very few studies on ADHD in children under 6 years old.

The main cause of OSAH in children is hypertrophy of the adenoids and tonsils, and the most rapid growth of the adenoids occurs between the ages of 3 to 6 years. A significant increase in tonsil growth occurs between the ages of 3 and 5 years, and growth continues until puberty, when they tend to shrink due to decreased immune function[5]. Thus, adenoid hypertrophy is apparent at 6 years of age, and adenoid hypertrophy is the inflection point.

Moreover, the author has found in previous studies[6] that the incidence of allergic rhinitis and otitis media differs between children with OSAHS under 6 years old and those over 6 years old. Therefore, in this paper, the children with OSAHS were divided into two age groups according to the dividing line of 6 years of age. The children with OSAHS in different age groups were retrospectively analyzed, and factors related to OSAHS plus ADHD were retrospectively analyzed.

Age group	Group	Gender		Chi-square	P
		Male N(%)	Female N(%)		
4-5 years	OSAHS	101 (62.35)	61 (37.65)	4.478	0.214
	OSAHS plus ADHD-I	8 (61.54)	5 (38.46)		
	OSAHS plus ADHD-HI	20 (68.97)	9 (31.03)		
	OSAHS plus ADHD-C	26 (81.25)	6 (18.75)		
6-11years	OSAHS	92 (71.31)	37 (28.68)	1.683	0.641
	OSAHS plus ADHD-I	18 (69.23)	8 (30.77)		
	OSAHS plus ADHD-HI	11 (61.11)	7 (38.89)		
	OSAHS plus ADHD-C	22 (78.57)	6 (21.43)		

Table 1: Basic characteristics of the sample.

Ther difference in the distribution of male and female children was not statistically significant between the two age groups. There were 236 children in the 4- to 5-year age group, and the ratio of males to females was 1.91:1. The proportion of children with OSAHS plus ADHD is 31.36% (74 in 236) in this age group, which was much higher than that in the general population of children. In addition, mixed ADHD was the most common type among both males and females (13.56%), followed by the hyperactive (12.29%) and attention deficit (5.50%) types.

There were a total of 201 children in the 6- to 11-year age group, and the ratio of males to females was 2.47:1. The proportion of childrenwith OSAHS plus ADHD is 35.82%, which was also significantly higher than that in the general population of children. For both males and females, mixed-type ADHD was the most common type (13.93%), followed by the attention deficit (12.94%) hyperactive (9.0%) types.

Age group	OSA-18 score	OSAHS (1)	OSAHS plus ADHD-I (2)	OSAHS plus ADHD-HI (3)	OSAHS plus ADHD-C (4)	F/H	P-value	Post hoc
4-5	Sleep disorders	16 (24)	20 (16)	17 (22)	20 (45)	22.77	<0.001	1<2, 1<4
	Physical symptoms	15 (23)	15 (10)	19 (13)	16 (18)	11.53	0.009	1<3
	Mood disorders	8 (15)	13.5 (15)	14 (15)	14 (17)	72.87	<0.001	1<2, 1<3, 1<4
	Daytime functioning	8 (16)	11 (6)	9 (11)	11 (11)	30.59	<0.001	1<2,1<4
	Impact on caregivers	16 (24)	14.5 (19)	20 (23)	20.5 (18)	14.53	0.002	1<4
	Total score	10 (23)	23 (25)	21 (13)	33 (22)	109.86	<0.001	1<2, 1<3, 1<4
6-11	Sleep disorders	14 (24)	15.5 (17)	15 (12)	21 (20)	12.52	0.006	1<4
	Physical symptoms	14 (20)	16 (18)	17 (12)	16 (19)	12.37	0.006	1<4
	Mood disorders	8 (16)	10.5 (18)	10 (6)	14 (16)	44.91	<0.001	1<4, 2<4
	Daytime functioning	8 (13)	10 (16)	9 (4)	12 (13)	36.44	<0.001	1<4, 2<4
	Impact on caregivers	15 (24)	16 (21)	12 (11)	21 (21)	17.09	<0.001	3<4, 1<4
	Total score	10 (38)	23 (18)	21 (5)	33 (33)	109.00	<0.001	1<2, 1<3, 1<4

Table 2: Comparison of OSA-18 scores among age groups.

Ages 4-5 years:

• Sleep disorder: the pure OSAHS group had lower scores than the OSAHS plus attention deficit-type ADHD and the OSAHS plus mixed ADHD group (P<0.001).

• Physical symptoms: the pure OSAHS group had lower scores than the OSAHS plus hyperactivity-type ADHD group (P=0.009).

• Mood disorder: the pure OSAHS group had lower scores than all patients with ADHD (P<0.001). Daytime functioning: The pure OSAHS group had lower scores than the OSAHS plus attention deficit-type ADHD and the OSAHS plus mixed ADHD groups (P<0.001).

• Impact on caregivers: the pure OSAHS group had lower scores than the OSAHS plus mixed ADHD group (P=0.002).

Ages 6 to 11 years:

• Sleep disorder: the pure OSAHS group had lower scores than the OSAHS plus mixed ADHD group (P=0.006).

• Physical symptoms: the pure OSAHS group had lower scores than the OSAHS plus mixed ADHD group (P=0.006).

• Emotional disorder: the pure OSAHS group and the OSAHS plus attention deficit-type ADHD group had lower scores than the OSAHS plus mixed ADHD group (P<0.001).

• Daytime functioning: the pure OSAHS group and the OSAHS plus attention deficit-type ADHD groups had lower scores than the OSAHS plus mixed ADHD groups (P<0.001).

• Impact on caregivers: the pure OSAHS group had lower scores than the OSAHS plus mixed ADHD group. The OSAHS plus hyperactive-type ADHD groups had lower scores than the OSAHS plus mixed ADHD group (P<0.001).

Age group, years	Parameters	OSAHS (1)	OSAHS plus ADHD-I (2)	OSAHS plus ADHD-HI (3)	OSAHS plus ADHD-C (4)	F/H	P-value	Post hoc
4-5	Dopamine (ng/L)	23.6 (206.75)	39.75 (167.98)	59.6 (144.92)	53 (178.75)	67.11	<0.001	1<2, 1<3, 1<4
	Norepinephrine (ng/L)	424 (1106.28)	496.5 (643)	430 (1258)	396.34 (1290.49)	2.67	0.445	\
	Dopamine/ norepinephrine	0.0637 (0.6875)	0.1126 (0.6649)	0.1834 (0.2823)	0.1487 (0.7676)	66.18	<0.001	1<2, 1<3, 1<4
6-11	Dopamine (ng/L)	28.5 (287)	33.9 (258.67)	58 (156.518)	56 (9.8)	8.75	0.033	1<3
	Norepinephrine (ng/L)	487 (1564.36)	361 (1132.21)	371 (1070.76)	409 (137)	8.44	0.038	\
	Dopamine/ norepinephrine	0.080 (0.658)	0.109 (0.787)	0.149 (0.372)	0.132 (0.043)	8.83	0.032	1<3

Table 3: Comparison of single amine oxidase A indexes in different groups.

For the children between 4 to 5 years old, dopamine level was significantly higher in the ADHD groups than in the pure OSAHS group (P<0.001). There were no statistically significant differences in norepinephrine between the two groups, but the ratios of dopamine/norepinephrine were significantly different (P<0.001), with the highest values in the hyperactive type, mixed type second, and pure OSAHS were the lowest.

For the children aged 6 to 11 years, the differences in levels of dopamine and norepinephrine as well as the ratio of dopamine/norepinephrine were all statistically significant (P<0.05). The pure OSAHS group had lower dopamine level and dopamine/norepinephrine ratio than the OSAHS plus hyperactive-type ADHD group.

Age group, years	Parameters	OSAHS (1)	OSAHS plus ADHD-I (2)	OSAHS plus ADHD-HI (3)	OSAHS plus ADHD-C (4)	H-value	P-value	Post hoc
4-5	AHI	7.81 (9.85)	9.63 (9.81)	9.65 (9.75)	12.65 (9.87)	39.71	<0.001	1<2, 1<3, 1<4
	SaO2	84 (34)	74.25 (31.4)	75.8 (30.8)	60.45 (52.1)	45.53	<0.001	1>2, 1>3, 1>4
6-11	AHI	7.73 (9.62)	9.17 (9.97)	8.01 (2.16)	11.84 (9.75)	36.44	<0.001	1<2, 1<4
	SaO2	84.7 (34.8)	79.8 (34.4)	78 (16.7)	61 (32.7)	29.94	<0.001	1>4, 2>4

Table 4: Comparison of sleep monitoring indicators among OSAHS groups.

Ages 4-5 years

OSAHS-related sleep disorder and hypoxia scores were lower in the children with pure OSAHS group than in those with OSAHS plus ADHD group (P<0.001).

Ages 6-11 years

OSAHS-related sleep disorder and hypoxia scores were lower in the children with pure OSAHS group than in those with OSAHS plus mixed-type and attention deficit-type ADHD group(P<0.001).

Discussion

ADHD is the most common psychiatric disorder in childhood with a global prevalence of approximately 3%. Boys are approximately 4 to 9 times more likely to be affected than girls. ADHD is not a disease caused by a single factor, but a syndrome caused by multiple factors, including biological, psychological and social factors. Children with ADHD have sleep problems such as late bedtimes, long sleep onset, easy awakening from sleep, and difficulty falling asleep after waking up. Goraya JS

showed that sleep respiratory disorder is a common symptom in children with ADHD[7]. Several studies have found a high incidence of OSA among ADHD patients. Sleep apnea may be related to attention deficits and hyperactivity in children with ADHD[8].

Both domestic and international studies report OSAHS prevalence of 2%-4% in children[9]. OSAHS cannot be effectively controlled and can have an important effect on children's physical and mental development[10]. Attention deficits have been found in 95% of OSA patients (adults and children). In a study by the National Institutes of Health, 26% of children aged 5-7 years with OSAHS were reported with mild ADHD[11]. When treating OSAHS and eliminating snoring, 81% of children with OSAHS combined with ADHD can be cured without treatment[11]. Sherwin et al. suggested that if snoring were effectively treated, 25% of ADHD cases would disappear[12]. An AHI >1 is considered abnormal and can exacerbate ADHD in children[13]. Even in children with an AHI <1 who snore, adenoidectomy can effectively improve the behavior and cognition issues associated with ADHD[11].

Currently, the prevalence of ADHD in China is 4.31% to 5.83% among school-age children. In the healthy population, the prevalence of ADHD declines with age. In this study, there were 236 children in the 4-5 age group. OSAHS combined with ADHD was significantly higher than the prevalence rate healthy children. OSAHS combined with ADHD accounted for 31.36% of them, a male-to-female ratio of 1.91:1. In addition, mixed ADHD was the most common type in both males and females (13.56%), followed by hyperkinetic-type ADHD (12.29%) and attention deficit-type ADHD (5.50%).

The total number of people in the 6-11 age group was 201, OSAHS combined with ADHD accounted for 35.82% of them, a male-to-female ratio of 2.47:1 (table 1). The occurrence of OSAHS combined ADHD is 35.82% in our study, which is significantly higher than that in the general population of children. For both males and females, the most common type of ADHD was mixed type (13.93%), the second most common was attention deficit type (12.94%), and hyperactivity type was the lease common (9.0%). The prevalence of ADHD in children with OSAHS is much higher than that in the ordinary children. The proportion of ADHD among children with OSAHS increases with age, caused maybe by the long duration of OSAHS. Longer exposure to periods of anoxia may have a greater influence on the brain, but the proportion of hyperactivity-type ADHD found in this study is consistent with the literature. Regardless of age, there were statistically significant differences in the OSA-18 sleep disorder scores, physical symptoms, mood disorders, and functional status during the day in the OSAHS plus ADHD group compared with the pure OSAHS group. The impact of the five component indicators was statistically significant; the OSAHS plus ADHD group had higher scores than the pure OSAHS group, indicating that children with ADHD were more severely affected by sleep disorders and poor quality of life (table 2).

Consistent with these findings, a study in the journal Sleep Monitoring found that children with OSAHS plus ADHD children had more respiratory events and lower oxygen saturation than children with OSAHS alone, and the difference was statistically significant. The children with OSAHS plus ADHD in both the youngest and oldest age groups were more severely affected than those with OSAHS alone (table 3). Some animal experiments have found that intermittent hypoxia can affect brain function, causing hyperactivity[14]. Because children are still growing and developing, their brains are more sensitive to hypoxia. Sleep disorders lasting 1 week or longer can cause emotional disorders or cognitive decline in humans[15]. Reports indicate that after surgical correction of the causes of hypoxia, attention deficit and hyperactivity improve[16]. Therefore, in children with OSAHS, more severe sleep disorder and hypoxia increase the likelihood that ADHD will develop. In OSAHS patients, disease progression and hypoxia can change the levels of dopamine and epinephrine in the prefrontal cortex, causing and/or aggravating cognitive and executive function damage and mood disorders, which plays a certain role in the pathogenesis of ADHD[17]. Neural biochemical studies have shown the occurrence of ADHD in children with deviations in dopamine, norepinephrine and a single amine central neurotransmitter, which are currently considered dopamine (DA), norepinephrine (NE) neurotransmitter metabolic imbalances. D-dopamine-hydroxylase is the enzyme converting dopamine into norepinephrine. When serum DBH decreases, dopamine/norepinephrine levels increase, leading to hyperactivity[18].

In 2010, Zhao et al.[19] found that there were no abnormalities in serum dopamine and norepinephrine levels in ADHD. We found that children aged 4 to 5 years with OSAHS plus ADHD had significantly higher dopamine levels than those with pure OSAHS ($P<0.001$). No statistically significant differences in

norepinephrine levels were observed between the two groups. Dopamine/norepinephrine had statistical significance (P<0.001), the highest hyperactivity type, mixed type second, and pure OSAHS. Among the children aged 6-11 years, the differences in dopamine and dopamine/norepinephrine all statistically significant among the groups (P<0.05), while the differences in norepinephrine were not statistically significant. In comparison, dopamine and dopamine/norepinephrine levels were lower in the OSAHS group than in the OSAHS plus hyperactivity-type ADHD group (table 4). These findings indicate that norepinephrine is not an independently influential factor, and only dopamine and the dopamine/norepinephrine index are indicators. Dopamine and norepinephrine can precisely reflect DβH activity; both are negatively correlated, meaning that when DβH activity is lower, the onset of ADHD is more likely. This result is in consistence with a previous study by YS Huang 18 and is increasingly apparent in ADHD.

The incidence of ADHD in our study is higher than 30% in children with OSAHS, which increases with age. This phenomenon may be associated with the longer course of OSAHS, the longer time of exposure to hypoxia and the more server influence on brain function. In children with OSAHS, more severe ADHD and anoxia (more breathing effort and lower oxygen saturation) results in lower dopamine - hydroxylase (DβH) activity, which lead to higher serum levels of dopamine/5 serotonin, greater dopamine/norepinephrine imbalance and increased hyperactivity. It can be assumed effectively increasing the activity of DβH can lead to the reduction or elimination of hyperactive-type ADHD.

This study investigated the factors related to ADHD in OSAHS, while children with ADHD alone were not included. The inclusion of these children would benefit this study and provide further support for our findings. This was a retrospective study, and prospective studies are needed to valid our findings.

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List of abbreviations:
Attention deficit hyperactivity disorder (ADHD); obstructive sleep apnea hypopnea syndrome (OSAHS); dopamine (DA); norepinephrine (NE); serotonin (5-HT); polysomnography (PSG); obstructive sleep apnea (OSA); obstructive apnea index (OAI); apnea hypopnea index (AHI); lowest oxygen saturation (SaO_2)

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