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Basic and clinical research on children snoring and obstructive sleep apnea syndrome

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Basic and clinical research on children snoring and obstructive sleep apnea syndrome

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The correlation between OSA-related quality of life and two mental statuses in adolescent Chinese patients with cleft palate: A comprehensive study

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Objectives: To analyze obstructive sleep apnea (OSA)-related quality of life (QoL), the statuses of depression and anxiety, and to reveal the correlation between OSA-related QoL and two mental statuses in Chinese adolescent patients with cleft palate (CP).

Methods: The Obstructive Sleep Apnea Questionaire-18 (OSA-18), the Generalized Anxiety Disorder Scale (GAD-7) and the Patient Health Questionnaire-9 (PHQ-9) were applied to assess OSA-related QoL and the statuses of anxiety and depression in Chinese adolescent patients with CP, respectively. Non-CP adolescents were also included in the control group. OSA-related QoL and the two mental statuses were compared between the study and control groups. The correlation between the OSA-related QoL and two mental statuses was estimated in Chinese adolescent patients with CP.

Results: A total of 8.7% patients showed a moderate or high impact of OSA on QoL, while all the adolescents from the control group showed little impact. The mean total OSA-18 score of the study group (36.261 ± 13.500) was significantly higher than the control (28.435 ± 8.934). The mean PHQ-9 scores of the study group and the control group were statistically different (3.957 vs. 2.113). The GAD-7 score in the study group was slightly higher than the control group (3.043 vs. 2.194), while the proportion of moderate-severe anxiety in the study group was relatively larger than that in the control group (6.5% vs. 1.6%). Moreover, there was a positive correlation between the OSA-related QoL and the statuses of anxiety and depression respectively, and the differences in GAD-7 and PHQ-9 scores between the moderate or high impact group and the little impact group were statistically significant.

Conclusion: Chinese adolescents with CP reported a rate of moderate or high impact of OSA on QoL of 8.7%, which was significantly higher than adolescents without CP. The OSA-related QoL was worse and depression was severer in Chinese CP adolescents than in the control, while anxiety and depression in Chinese CP adolescents were associated with OSA-related QoL.

KEYWORDS

cleft palate, OSA-related QoL, sleep-disordered breathing, anxiety, depression, OSA-18, GAD-7, PHQ-9

Introduction

Cleft palate (CP) is one of the most common congenital abnormalities, which can lead to dysfunction of speech, breathing, and swallowing of the patients due to the abnormal anatomical structure of the palate and pharynx (1). CP might also bring nasal deformities, retrusive midface or small pharyngeal airway as the patients growing up, and herein exposes them to a high risk of obstructive sleep apnea (OSA) (2). It was found that the posterior airway space in adolescent patients after palatoplasty showed certain characteristics of OSA (3), which could affect the sleep-related breathing and related quality of life (QoL).

Sleep-disordered breathing (SDB), like OSA, could bring neuropsychiatric effects and adverse health consequences (4, 5), which could greatly affect the QoL of patients. It was reported that OSA had a correlation with mental disorders like anxiety and depression (6). Besides, it was also shown that anxiety and depression could affect sleep (7). Although sleep-related breathing problems had been found in patients with CP (8), their OSA-related QoL had not received due attention, and there was a lack of relevant study in Chinese patients with CP.

In this study, we sought to compare the OSA-related QoL, and the statuses of depression and anxiety, between patients and control adolescents, and ulteriorly demonstrate the correlation between the OSA-related QoL and these two mental statuses, anxiety and depression. The Obstructive Sleep Apnea Questionaire-18 (OSA-18) has been widely used to assess QoL in children with SDB in previous studies, in children with macroglossia and adenotonsillar hypertrophy for example (9, 10), and therefore was considered as a valid measure of health-related QoL (11). In our study, OSA-18 was applied to assess the QoL in children with CP, while the generalized anxiety disorder 7-item (GAD-7) scale and the Patient Health Questionnaire-9 (PHQ-9) were applied to assess the statuses of anxiety and depression. Based on this study, we tried to provide a theoretical basis for cleft palate care and possible psychological intervention.

Materials and methods

Subjects

Chinese Patients with a history of cleft palate hospitalized in West China Hospital of Stomatology, Sichuan University, between July 2019 and January 2021 were incorporated in the study group.

Inclusion criteria of the study group were as follows:

(1) Patients with cleft palate;
(2) Patients who had no other syndromic diseases;
(3) Patients who underwent palatoplasty at the age of 6 months to 2 years;
(4) Patients without secondary surgery of cleft palate or other types of speech surgery like posterior pharyngeal flap or orthognathic surgery at the time of data collecting;
(5) Patients aged above 10 (12) and under 17 (13).

Inclusion criteria of the control group were as follows:

(1) Individuals who had cone-beam computed tomography scan for other dental treatments;
(2) Individuals with normal speech and without significant nasal septal deviation or micromandible or other significant airway diseases;
(3) Individuals aged above 10 and under 17.

A total of 46 patients were enrolled (Mean age: 13.41 ± 2.14 years), while a total of 62 normal adolescents were enrolled (Mean age: 13.84 ± 0.91 years). Among the study group, 63.0% were males; 87.0% had cleft lip and palate, and 13.0% had cleft palate only; 26.1% were diagnosed with velopharyngeal insufficiency. In the control group, 54.8% were males.

The study was approved by the Ethics Committee of West China Hospital of Stomatology, Sichuan University (No. WCHSIRB-D-2016-084R1). All the parents of the patients enrolled in the study provided written informed consents.

Assessment of OSA-related QoL

The Obstructive Sleep Apnea Questionaire-18 (OSA-18) was used to assess the OSA-related QoL, which contained 18 items rated from 1 to 7 with a Likert scale. The 18 items were grouped into 5 domains: sleep disturbance, physical suffering, emotional distress, daytime problems, and caregiver concerns. A total score above 60 suggested that the sleep disorder had a moderate or high impact on QoL (14). Good reliability and validity of Chinese-version OSA-18 have been validated in patients aged 2–18 years old (15), and OSA-18 has been used in adolescent patients with cleft palate (2). The questionnaire was filled in by the patients' parents or legal guardians independently based on the situation of their children in the past 4 weeks (16).

Assessment of anxiety

The Generalized Anxiety Disorder 7-item (GAD-7) scale was given to adolescents themselves to assess their anxiety status over the last 2 weeks with 7 items graded on a 4-point Likert scale as 0 (not at all), 1 (several days), 2 (more than half the days), and 3 (nearly every day). The subjects were divided into normal (0–4), mild (5–9), moderate (10–14) and severe (15–21) according to the total score. Chinese-version

GAD-7 has been widely used in Chinese population, notably in the cleft field (17), and has shown good reliability and validity among Chinese adolescents aged 10–17 years old (12).

Assessment of depression

The Patient Health Questionnaire-9 (PHQ-9) was applied to assess depression status in the past 2 weeks, which consisted of 9 items on a 4-point scale ranging from 0 (not at all) to 3 (nearly every day). A total score of 10 points was considered to be the dividing line between depression and non-depression. PHQ-9 has been widely used to assess depressive symptoms in patients with specific diseases (18–20), and the reliability and effectiveness of PHQ-9 have been validated in Chinese adolescents aged 11–17 years old (21), and has been applied to autistic patients aged 10–18 in Singapore (22).

In this study, all subjects received questionnaires of the Chinese version and to ensure that each item was fully understood, questionnaires were completed under the guidance of trained volunteers.

Statistical analysis

Statistical analysis was performed using SPSS 26.0 (IBM Corp., Armonk, NY, USA), and count data were expressed as the mean ± standard deviation (SD). Mann–Whitney *U* test was used to compare the two independent variables between groups, and categorical variables (impact on QoL) were compared between the groups using Fisher exact test, while Spearman's rank correlation was used to estimate the correlation among the OSA-related QoL, anxiety status and depression status. Shapiro-Wilk demonstrated non-normal distribution of those statistics. ***P***-values <0.05 were statistically significant.

Results

OSA-related QoL in the study and control groups

The mean total OSA-18 scores of the study and control groups were 36.261 and 28.435 points respectively, and differences in total OSA-18 score, domains including emotional distress, daytime problems and caregiver concern and several items of OSA-18 (OSA-18-8/10/12/15/16/17/18) were statistically significant, among which the mean score of the study group was higher than that of the control group (**Table 1**). 8.7% of the total OSA-18 scores were above 60 in the study group, showing moderate or high impact on QoL, while all the adolescents from the control group showed little impact, which was statistically significant (**Table 2**).

Anxiety status in the study and control groups

There was no statistically significant difference in GAD-7 total score and scores of each item between the study group and the control group. However, the mean GAD-7 total score in the study group was slightly higher than the control group (3.043 vs. 2.194) (**Table 3**). Besides, the proportion of moderate-severe anxiety in the study group was larger than in the control group (6.5% vs. 1.6%) (**Table 4**).

Depression status in the study and control groups

The mean total PHQ-9 scores of the study group and the control group were statistically different (3.957 vs. 2.113), and the mean scores of items "Poor appetite or overeating" and "Feeling bad about yourself or that you are a failure or have let yourself or your family down" showed statistical difference (**Table 5**).

Correlation analysis between the OSA-related QoL and the statuses of anxiety and depression

There was a positive correlation between the OSA-related QoL and the statuses of anxiety and depression, respectively. The total OSA-18 score and domains including sleep disturbance, emotional distress and caregiver concern were all positively correlated with GAD-7 scores, while the total OSA-18 score and domains including sleep disturbance, emotional distress, daytime problems and caregiver concern were positively correlated with PHQ-9 scores (**Table 6**).

The analysis of the impact situations of OSA-related QoL on mental status

The differences of GAD-7 and PHQ-9 scores between the moderate or high impact group and the little impact group were statistically significant, which demonstrated the influence of OSA-related QoL on these two mental statuses (**Table 7**).

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TABLE 1 The OSA-18 scores of the study group and control group.

Variable	Mean ± SD		*P*-value
	The study group	The control group	(Study vs. Control)
OSA-18 components			
Total OSA-18 score	36.261 ± 13.500	28.435 ± 8.934	0.001**
Sleep disturbance	5.674 ± 2.271	5.161 ± 1.857	0.168
OSA-18-1: Loud snoring	1.565 ± 0.958	1.339 ± 0.767	0.143
OSA-18-2: Breath holding/pauses	1.152 ± 0.666	1.145 ± 0.507	0.591
OSA-18-3: Choking or gasping	1.217 ± 0.593	1.226 ± 0.638	0.728
OSA-18-4: Fragmented sleep	1.739 ± 1.084	1.452 ± 0.783	0.176
Physical suffering	6.848 ± 3.326	6.081 ± 2.706	0.227
OSA-18-5: Mouth breathing	1.717 ± 1.109	1.887 ± 1.415	0.766
OSA-18-6: Frequent colds or URIs	1.783 ± 1.246	1.597 ± 0.999	0.500
OSA-18-7: Rhinorrhea	2.000 ± 1.333	1.581 ± 1.001	0.075
OSA-18-8: Dysphagia	1.348 ± 0.737	1.016 ± 0.127	0.001***
Emotional distress	5.587 ± 2.325	4.790 ± 2.362	0.022*
OSA-18-9: Mood swings or tantrums	2.130 ± 1.240	1.952 ± 1.324	0.23
OSA-18-10: Aggression/hyperactivity	1.870 ± 1.185	1.452 ± 1.003	0.009**
OSA-18-11: Discipline problems	1.587 ± 1.002	1.387 ± 0.610	0.508
Daytime problems	7.196 ± 3.976	5.677 ± 2.597	0.048*
OSA-18-12: Daytime drowsiness	1.913 ± 1.411	1.355 ± 0.630	0.013*
OSA-18-13: Poor attention span	2.674 ± 1.752	2.194 ± 1.502	0.136
OSA-18-14: Difficulty awakening	2.609 ± 1.807	2.129 ± 1.152	0.326
Caregiver concern	10.957 ± 5.617	6.726 ± 3.825	0.000***
OSA-18-15: Caregiver worried about child's health	4.239 ± 2.110	2.371 ± 1.776	0.000***
OSA-18-16: Caregiver concerned child does not have enough air	2.783 ± 2.250	1.645 ± 1.427	0.005**
OSA-18-17: Caregiver missed activities	1.935 ± 1.652	1.306 ± 0.781	0.028*
OSA-18-18: Caregiver frustration	2.000 ± 1.700	1.403 ± 0.983	0.027*

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ by Mann–Whitney *U* test.

TABLE 2 Comparison of the impact of OSA on QoL between the study group and control group.

	The study group	The control group	*P*-value
Moderate or high impact	4 (8.7%)	0 (0%)	0.030*
Little impact	42 (91.3%)	62 (100%)	
Total	46	62	

*$P < 0.05$ by Fisher's Exact Test.

Discussion

Cleft palate may lead to nasal deformities, retrusive midface or small pharyngeal airway, which bring a high risk of OSA (2). OSA-related symptoms, such as snoring and noisy breathing during sleep were often reported in children with CP (3). Even after palatoplasty, upper airway dimensions were still reduced in patients with CP (23). OSA had a significant impact on quality of life, which could lead to anxiety and depression (24, 25) and result in adverse societal and individual correlates (26). In this study, we aimed to analyze OSA-related QoL and the statuses of depression and anxiety, and to further reveal the correlation between OSA-related QoL and two mental statuses in Chinese adolescent patients with CP.

According to OSA-18 results, we found that the average OSA-18 score of Chinese adolescent patients with CP was higher than the controls, which might reveal that adolescents with CP were at higher risk of OSA, consistent with the results evaluated by the Pediatric Sleep Questionnaire (PSQ) and polysomnography (PSG) in the previous studies (27, 28). The rate of moderate or high impact of OSA on QoL in children with CP (8.7%), which was approximately consistent with previous studies (9.5%) (2), was significantly higher than that of the control group (0%). As for the statistically significant domains of emotional distress, daytime problems and caregiver concern in the control group, we found that the influence of OSA on QoL in patients with CP was more manifested in emotion, behavior and the influence on

TABLE 3 The GAD-7 scores of the study group and control group.

Variable	Mean ± SD		*P*-value
	The study group	The control group	(Study vs. Control)
Total GAD-7 score	3.043 ± 3.608	2.194 ± 2.851	0.080
GAD-7-1: Feeling nervous, anxious or on edge	0.565 ± 0.620	0.387 ± 0.554	0.104
GAD-7-2: Not being able to stop or control worrying	0.304 ± 0.628	0.306 ± 0.561	0.751
GAD-7-3: Worrying too much about different things	0.391 ± 0.774	0.387 ± 0.554	0.445
GAD-7-4: Trouble relaxing	0.370 ± 0.572	0.306 ± 0.531	0.553
GAD-7-5: Being so restless that it is hard to sit still	0.348 ± 0.737	0.210 ± 0.410	0.597
GAD-7-6: Becoming easily annoyed or irritable	0.696 ± 0.840	0.419 ± 0.588	0.103
GAD-7-7: Feeling afraid as if something awful might happen	0.370 ± 0.679	0.177 ± 0.385	0.152

TABLE 4 Severity of anxiety in the study and control groups.

	Total	Normal		Mild anxiety		Moderate and severe anxiety	
		Number	Percentage	Number	Percentage	Number	Percentage
The study group	46	38	82.60%	5	10.90%	3	6.50%
The control group	62	49	79.00%	12	19.40%	1	1.60%

TABLE 5 The PHQ-9 scores of the study group and control group.

Variable	Mean ± SD		*P*-value
	The study group	The control group	(Study vs. Control)
Total PHQ-9 score	3.957 ± 4.685	2.113 ± 2.931	0.018*
PHQ-9-1: Little interest or pleasure in doing things	0.435 ± 0.720	0.306 ± 0.465	0.552
PHQ-9-2: Feeling down, depressed, or hopeless	0.391 ± 0.649	0.306 ± 0.499	0.703
PHQ-9-3: Trouble falling or staying asleep, or sleeping too much	0.652 ± 0.948	0.274 ± 0.485	0.053
PHQ-9-4: Feeling tired or having little energy	0.478 ± 0.752	0.258 ± 0.441	0.191
PHQ-9-5: Poor appetite or overeating	0.630 ± 0.799	0.290 ± 0.524	0.018*
PHQ-9-6: Feeling bad about yourself or that you are a failure or have let yourself or your family down	0.609 ± 1.000	0.226 ± 0.525	0.040*
PHQ-9-7: Trouble concentrating on things, such as reading the newspaper or watching television	0.283 ± 0.688	0.145 ± 0.355	0.562
PHQ-9-8: Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	0.326 ± 0.732	0.177 ± 0.497	0.399
PHQ-9-9: Thoughts that you would be better off dead or of hurting yourself in some way	0.152 ± 0.420	0.129 ± 0.338	0.949

*$P < 0.05$ by Mann–Whitney *U* test.

caregivers than the physical symptoms, which coincided with previous studies in children with CP (29–31). Compared with non-cleft, the clinical symptoms of OSA in children with CP was similar (29). However, aggressive behavior and defiant temper were confirmed in children with CP under the influence of sleep-disordered breathing (30), and daytime functional problems such as daytime sleepiness and inattention were reported in children with CP in previous studies (31).

Our research further confirmed these conditions not only in children but also in adolescents with CP. As for the caregiver concern dimension, the sleep-disordered breathing problems of children with CP were often reported by their parents (3), and under greater pressure, the quality of life and psychology of parents of children with CP were affected simultaneously (32).

Our results showed that 6.5% of adolescent patients with CP were in moderate or severe anxiety, compared with 1.6% in the control group. However, no significant difference in total GAD-7 scores and scores of each item between the study group and the control group was found, which was consistent with the results of previous studies that there was no significant

TABLE 6 Correlation analysis among the OSA-18, GAD-7 and PHQ-9 in the study group.

Variable	GAD-7		PHQ-9	
	ρ	*P*-value	*P*	*P*-value
OSA-18 components				
Total OSA-18 score	0.339	0.021*	0.461	0.001**
Sleep disturbance	0.317	0.032*	0.503	0.000***
Physical suffering	0.138	0.359	0.289	0.051
Emotional distress	0.307	0.038*	0.394	0.007**
Daytime problems	0.250	0.094	0.457	0.001**
Caregiver concern	0.333	0.024*	0.389	0.008**

*$P < 0.05$, ** $P < 0.01$, ***$P < 0.001$ by Spearman's rank correlation.

TABLE 7 The GAD-7 and PHQ-9 scores of different impact situations of OSA-related QoL in the study group.

Variable	Mean ± SD		*P*-value
	Moderate or high impact	Little impact	
GAD-7	7.000 ± 4.690	2.667 ± 3.318	0.028*
PHQ-9	10.250 ± 4.992	3.357 ± 4.247	0.014*

*$P < 0.05$ by Mann–Whitney *U* test.

difference in life satisfaction and anxiety between patients with CP and the non-CP control group (17, 33), but the proportion of patients with CP reporting anxiety problems was higher than that of the control group (34).

In contrast to anxiety status, there were significant differences in total PHQ-9 scores screening depression between the study group and the control group. As some studies have shown, compared with healthy children, depression in children with CP was more common (35). Items that demonstrated statistically significant difference were "Poor appetite or overeating" and "Feeling bad about yourself or that you are a failure or have let yourself or your family down". Patients with CP had difficulty chewing, especially biting hard food (36), and showed a more negative self-awareness (37), which might explain why the study group showed higher scores than the control in those items.

It used to be thought that the anxiety and depression of patients with CP mainly came from their abnormal appearance and pronunciation (38). However, our study reported that OSA-related QoL were also associated with anxiety and depression in Chinese adolescent patients with CP. Beyond this, the statuses of anxiety and depression between the moderate or high impact group and the little impact group of OSA-related QoL showed statistical significance. Previous studies have confirmed the relationship between OSA and the statuses of anxiety and depression (6, 39), and the same conclusion was drawn in Chinese adolescent patients with CP in our study.

The results showed that anxiety and depression were correlated with a number of domains of OSA-related QoL. However, there was no significant correlation between the physical suffering dimension and the statuses of anxiety and depression, which might be interpreted as, compared to the discomfort caused by sleep breathing symptoms, the psychological impact of CP was more from the mental and behavioral problems caused by it. The emotional distress dimension of OSA-18 scale was significantly correlated with GAD-7 and PHQ-9 scales, which reflected the homogeneity of the three scales in evaluating psychological status. It was also found that the caregiver concern dimension had significant correlation with GAD-7 and PHQ-9 scales. Other studies have shown that the life quality of parents of children with CP were relatively poor (32), while this study showed that this influence may be mutual. The stress and worries from parents were also related to the psychological status of children, social support and correct coping strategies being beneficial to alleviate this influence (40). Interestingly, depression symptoms were uniquely associated with daytime problems domain, which meant that children's OSA-related negative behavior during the day led to depression rather than anxiety. It might be explained that sleep may have etiologically distinct and directional associations with anxiety and depression (41).

There were some limitations in our study. The sample size should be enhanced in the future. This study was conducted only in a stomatological hospital in western China. Also, no conclusion could be drawn on the direction of causality because of the study type of cross-sectional study, and there was only scale measurement focusing on QoL, lacking objective sleep measurement. Another limitation that should be mentioned is that OSA-18 is a caregiver-administered tool based on targeted discussions with caregivers of children with OSA (16), but studies have shown discrepancies in patients vs. parents' perceptions of their conditions (42–44). Thus, further study is needed with a suitable patient-administered tool for screening OSA.

Conclusion

Chinese adolescents with CP reported a prevalence of rate of moderate or high impact of OSA on QoL of 8.7%, which was significantly higher than adolescents without CP. The OSA-related QoL was worse and depression was severer in Chinese CP adolescents than the control. Anxiety and depression in Chinese CP adolescents were associated with OSA-related QoL.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of West China Hospital of Stomatology, Sichuan University (No. WCHSIRB-D-2016-084R1). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

ZX and CY contributed equally to this work. ZX, CY, YZ, YY, WX and YZ contributed to the collection of data. ZX, CY, YZ, and TC analyzed the data. ZX, CY, BS, HH and CG contributed to writing and revising the paper. BS, HH and CG supervised the research. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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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Comparison of short-term recovery in children with obstructive sleep apnea undergoing tonsillotomy vs. tonsillectomy

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Objectives: To compare the pain levels, degrees of pharyngeal swelling, and weight loss after tonsillectomy vs. tonsillotomy in children clinically diagnosed with obstructive sleep apnea (OSA) over the first seven postoperative days, and to determine which procedure was associated with better recovery in the early postoperative period.

Methods: Between April 2021 and December 2021, 121 children with OSA (80 males and 41 females), ranging from 3 to 12 years of age with an average age of 6.7 years, were prospectively enrolled in this study conducted at Zhengzhou Central Hospital Affiliated to Zhengzhou University. The patients were randomly divided into two groups: a tonsillotomy group with 63 cases (40 males and 23 females) and a tonsillectomy group with 58 cases (40 males and 18 females). The patients' pain levels [as indicated by Parents' Postoperative Pain Measure (PPPM) scores] and degrees of pharyngeal swelling were recorded for seven days postoperatively, and the patients' body weights were recorded on postoperative day seven.

Results: In the tonsillotomy group, the PPPM scores were the highest on the day of surgery and on the first postoperative day; the patients' pain levels gradually decreased.The PPPM scores in the tonsillectomy group were higher than those in the tonsillotomy group from the day of surgery to the seventh postoperative day ($p < 0.05$). The degree of pharyngeal swelling was lower in the tonsillotomy group than in the tonsillectomy group. Weight loss was lower in the tonsillotomy group than in tonsillectomy group on the 7th day after surgery ($p < 0.05$). On the fifth, sixth, and seventh postoperative days, compared with preschool children, school-age children who had undergone tonsillotomy experienced more pain relief than those who had undergone tonsillectomy ($p < 0.05$).

Conclusion: Children with OSA experienced less pain, less pharyngeal swelling, and less weight loss with tonsillotomy than with tonsillectomy. On the fifth, sixth, and seventh postoperative days, compared with preschool children, tonsillotomy in school-age children is more advantageous in school-age children.

KEYWORDS

child, coblation, tonsillotomy, tonsillectomy, pain

Introduction

Obstructive sleep apnea (OSA) refers to a series of pathophysiological changes caused by frequent partial or total upper airway obstruction during sleep. The common cause is tonsil and/or adenoid hypertrophy (1, 2). Tonsillectomy and/or adenoidectomy are the treatment methods. After tonsillectomy, patients suffer from long-lasting severe pain. With the development of minimally invasive technologies, such as plasma and ultrasonic scalpels, in Western countries, tonsillotomy has gradually replaced tonsillectomy for the treatment of OSA in children (3, 4). In this study, continuous observations and comparisons of pharyngeal pain were performed to investigate the changes in pain levels after the two surgical procedures.

Patients and methods

Study subjects

This prospective study involved patients undergoing tonsil and adenoid surgery for OSA at Zhengzhou Central Hospital Affiliated to Zhengzhou University from April 2021 to December 2021. The inclusion criteria were (1) the diagnostic criteria of the Chinese Guideline for the Diagnosis and Treatment of Childhood Obstructive Sleep Apnea (2020) (5), (2) Before deciding on surgery, 90.3% of patients received regular conservative treatment. Complete preoperative polysomnography, OSA diagnosis, and snoring with mouth breathing during sleep, and (3) in line with the indications for tonsillectomy and adenoidectomy, tonsils of two degrees or more, and electronic nasopharyngoscopy or computed tomography indicating pathological adenoid hyperplasia(the pathological hypertrophy of adenoid is defined as 2/3 or more of the nostril after obstruction by adenoid tissue under nasal endoscopy or CT shows that A/N is greater than or equal to 0.7). The exclusion criteria were (1) recurrent tonsillitis (more than seven times over the previous year or more than five times per year for two consecutive years or more than three times per year for three consecutive years), (2) craniofacial deformity, (3) bleeding diathesis(Hemophilia, VK deficiency, immune thrombocytopenia, etc), (4) immunodeficiency, and (5) acute tonsil infection.

According to the inclusion and exclusion criteria, 121 patients (80 males and 41 females) were included in the study. Sample size calculation for the study: n1 = n2 = 4[(t a/2 + t ß)2 S2]/δ2. The patients' ages ranged from 3 to 12 years, and their average age was 6.7 years.

The patients were randomly divided into a tonsillotomy group and a tonsillectomy group. The tonsillotomy group included 63 cases (40 males and 23 females) with an average age of 6.6 years. Among them, 30 children were of preschool age (3–6 years old), and 33 were of school age (7–12 years old). The tonsillectomy group consisted of 58 cases (40 males and 18 females) with an average age of 6.9 years. Among them, 26 children were of preschool age, and 32 were of school age. There were no significant differences in baseline data, such as age, gender, and body mass index, between the two groups (all $p > 0.05$; **Table 1**). Informed consent was obtained from all patients' legal guardians. This study was approved by the hospital's ethics committee, The detailed number of the ethical application process: 202080.

Surgical procedures

Under general anesthesia and endotracheal intubation, all patients were placed in the supine position. An open mouth gag was used to fully expose the oropharynx. A low-temperature plasma system was used to assist in the operation. The nasopharynx was exposed through the oropharynx, and the adenoids were removed under the guidance of a 70° endoscope. In the tonsillotomy group, low-temperature plasma was used to ablate the tonsils, layer by layer, from their upper pole surface to the tonsillar fossa's thin layer of tonsil tissue. In the tonsillectomy group, low-temperature plasma was used to completely remove the tonsils along the tonsillar capsule.

Pain

The Parents' Postoperative Pain Measure (PPPM) is mainly used to assess pain-related behavioral changes in children aged 1–12 years (6) and includes 15 items:

1. Is the child more likely to complain than usual?
2. Is the child crying more than usual?
3. Is the child playing less than usual?
4. Does the child not enjoy doing what they usually do?
5. Is the child more anxious than usual?
6. Is the child quieter than usual?
7. Is the child less energetic than usual?
8. Is the child eating less than usual?

TABLE 1 Basic demographic information on the two patient groups.

Variable	Tonsillotomy group ($n = 63$)	Tonsillectomy group ($n = 58$)	χ^2/t	*P*
Sex, *n*			0.404 (χ^2)	0.525
Male	40	40		
Female	23	18		
Age (years), mean ± SD	6.57 ± 2.18	6.95 ± 2.59	−0.869 (t)	0.387
Body mass index, mean ± SD	0.65 ± 0.17	0.64 ± 0.18	0.334 (t)	0.739

9. Does the child cover the painful area?
10. Does the child refuse to eat?
11. Is the child afraid to touch the painful area?
12. Is the child groaning more than usual?
13. Does the child prefer to be close to you?
14. Does the child take drugs that are usually refused?
15. Is the child's face redder than usual?

Each item is answered with a "yes" or a "no." A "yes" corresponds to 1 point, while a "no" corresponds to zero points. The points are then added to give a total score. The total score ranges from 0 to 15. A score of ≥6 indicates severe pain. The patients' parents completed the PPPM daily from the day of surgery (Day 0) to the seventh postoperative day (Day 7).

Degree of pharyngeal swelling

Pharyngeal swelling from Day 0 to Day 7 was scored as follows: 0: no swelling of the palatopharyngeal arch, palatoglossal arch, or uvula; 1: edema limited to the area around the tonsillar fossa; 2: edema spread around the tonsillar fossa and soft palate, but no swelling of the uvula; 3: edema spread around the tonsillar fossa, soft palate, and uvula, but relatively normal shape of the uvula; 4: edema spread around the tonsillar fossa, soft palate, and uvula, and uvula swollen to a spherical shape.

Weight

Each participant's body weight was recorded before surgery and 7 days after surgery.

Statistical analysis

IBM SPSS Statistics 22.0 software was used for the statistical analysis. The Shapiro–Wilk test was used to assess data normality. Age, BMI, PPPM scores of patients in the two groups on the day of surgery, the first, second day after surgery, the degree of pharyngeal swelling on the day of surgery, the first, second, third day after surgery were in line with normal distribution, the normal distribution were expressed as means ± standard deviations between the two groups, and was compared with the independent-samples *t*-test. The chi-square test was used for gender data, P50 (P25, P75) was used to measure the PPPM score of pharyngeal pain on the third, fourth, fifth, sixth and seventh days after surgery, the degree of pharyngeal swelling on the fourth, fifth, sixth and seventh days after surgery, and the change of body weight. Mann–whitney *U* test was used to compare the pain scores at each time point between the two groups. Kruskal–wallis test was used to compare pain scores at each time point between multiple groups, and $p < 0.05$ was considered statistically significant.

Results

Pain

The PPPM scores from Day 0 to Day 7 were lower in the tonsillotomy group than in the tonsillectomy group (**Table 2**).

Degree of pharyngeal swelling

In both groups, swelling of the pharyngeal cavity was greatest on Days 0 and 1 and gradually decreased from Day 2 to Day 7. The tonsillotomy group exhibited significantly less swelling than the tonsillectomy group (**Table 3**).

Weight

Compared with the preoperative weights, both groups had lost weight on the 7th postoperative day. Body weight decreased by 1 (0, 1.5) kg in the tonsillotomy group and by 2 (1.43, 2.5) kg in the tonsillectomy group. The difference in weight change between the two groups was statistically significant.

Pain in preschool and school-age children

The two groups of patients were divided into 4 groups according to age: preschool tonsillotomy group, preschool tonsillectomy group, school-age tonsillotomy group, and school-age tonsillectomy group. On the day of surgery and on the first, second, third, and fourth postoperative days, there

TABLE 2 Pharyngeal pain (PPPM scores) comparisons between the tonsillotomy and tonsillectomy groups.

Day	Tonsillotomy group ($n = 63$)	Tonsillectomy group ($n = 58$)	t/z	*P*
D0	4.29 ± 1.38	7.60 ± 1.38	−13.15 (t)	0.000
D1	3.40 ± 1.77	7.19 ± 1.61	−12.259 (t)	0.000
D2	1.63 ± 1.22	5.72 ± 1.89	−14.19 (t)	0.000
D3	2 (0,2)	4 (3,5.25)	−7.610 (z)	0.000
D4	2 (0,2)	4 (2,6)	−7.154 (z)	0.000
D5	1 (0,2)	3 (2,3)	−7.076 (z)	0.000
D6	1 (0,2)	2 (2,4)	−4.075 (z)	0.000
D7	0 (0,1)	2 (2,4)	−4.138 (z)	0.000

TABLE 3 Comparisons of pharyngeal swelling between the tonsillotomy and tonsillectomy groups.

Day	Tonsillotomy group ($n = 63$)	Tonsillectomy group ($n = 58$)	t/z	P
D0	2.14 ± 0.64	3.66 ± 0.66	−12.717 (t)	0.000
D1	1.70 ± 0.89	3.52 ± 0.77	−11.914 (t)	0.000
D2	0.87 ± 0.63	2.78 ± 0.89	−13.531 (t)	0.000
D3	0.63 ± 0.57	1.93 ± 0.95	−9.136 (t)	0.000
D4	1 (0,1)	2 (1,3)	−6.856 (z)	0.000
D5	1 (0,1)	1 (1,2)	−5.421 (z)	0.000
D6	0 (0,1)	1 (1,2)	−5.583 (z)	0.000
D7	0 (0,1)	1 (1,2)	−5.290 (z)	0.000

were statistically significant differences in the PPPM scores between the preschool tonsillotomy and preschool tonsillectomy groups ($p < 0.05$). There were also statistically significant differences between the PPPM scores of the school-age tonsillotomy and school-age tonsillectomy groups on the same days ($p < 0.05$). On postoperative days five, six, and seven, there were no statistically significant differences between the PPPM scores of the preschool tonsillotomy group and those of the preschool tonsillectomy group ($p > 0.05$); however, there were statistically significant differences between the PPPM scores of the school-age tonsillotomy group and those of the school-age tonsillectomy group ($p < 0.05$), as shown in Table 4 and Figure 1.

Discussion

OSA is a common disease among children. If not treated, it may cause serious complications, such as growth retardation, craniofacial deformity, and cognitive impairment (7). Adenoidectomy and/or tonsillectomy are the first-choice treatments (8, 9). Tonsillectomy is the traditional surgical method, but with the development of low-temperature plasma, lasers, and ultrasonic scalpels, tonsillotomy is increasingly used for the treatment of OSA in children. Several studies have shown that there is no significant difference in long-term efficacy between tonsilloctomy and tonsillectomy (6, 10–12).

In this study, we continuously observed the changes in pain and swelling of the pharyngeal cavity in the tonsillectomy and tonsillectomy groups over seven postoperative days and found that the PPPM scores in both groups were highest on the day of surgery and on the following day. Mild pain (PPPM < 6) from the day of tonsilloctomy surgery to the second day after surgery, The tonsillectomy group, patients exhibited severe pharyngeal pain (PPPM ≥6) on the first two days. Likewise, pharyngeal swelling was most severe on the first two days after the operation in both groups. The postoperative inflammatory response is related to swelling of the pharyngeal cavity caused by the release of inflammatory factors within 48 h (13). With the gradual reduction in the inflammatory response and edema, the pain begins to wane. The pain levels in the tonsillectomy group were mild (PPPM ≤4) from Day 3 to Day 7. The pain levels in the tonsillotomy group were significantly lower, and there was no obvious pain from Day 4 onward. This is because tonsillectomy was performed along the Capsule of tonsil, and the glossopharyngeal nerve and vagus nerve sensory fibers were densely present in the subcapsular muscle layer of the the tonsillar fossa, leading to stronger stimulation of the muscularis nerve. Navaneethan et al. (14) reported that the depth of thermal damage to tissue caused by a plasma radiofrequency knife was 0.7–0.8 mm. Tonsillotomy, on the other hand, retains part of the tonsil tissue, which acts as a surgical barrier, reducing neuromuscular stimulation and pain.

In this study, the patients The patients in the tonsillotomy group and the tonsilletomy group were divided into two subgroups of preschool age and school age according to age. On the 5th, 6th and 7th days after operation, compared with preschool children, partial tonsillectomy in school age children was more painful than total tonsillectomy. This may be because although patients aged 7–12 years have not yet developed chronic tonsillitis, as age increases, the frequency of tonsillitis may also increase. postoperative pains of school age children was obvious. Preoperative anxiety may also aggravate

TABLE 4 Comparisons of pharyngeal pain (PPPM scores) in preschool and school-age children between the tonsillotomy and tonsillectomy groups.

Day	Preschool-age Tonsillotomy ($n = 30$)	Preschool-age tonsilletomy ($n = 26$)	School-age tonsillotomy ($n = 33$)	School-age tonsilletomy ($n = 32$)	p
D0	4 (4,5)	8 (6,8)	4 (4,5)	8 (8,9)	0.000
D1	4 (2,4)	8 (5.5,8)	4 (2,4)	8 (7,8)	0.000
D2	2 (0,2)	(3.75,6.25)	2 (1,2)	6 (6,7)	0.000
D3	1 (0,2)	4 (2,5.25)	2 (0,2)	4 (3.25,5.5)	0.000
D4	0 (0,1.25)	2 (2,3.25)	0 (0,2)	2 (2,4)	0.000
D5	0 (0,1)	2 (0,2)	0 (0,2)	2 (2,3.75)	0.000
D6	0 (0,1)	0 (0,2)	0 (0,1)	2 (1,2.75)	0.000
D7	0 (0,1)	0 (0,2)	0 (0,1)	2 (1,2.75)	0.000

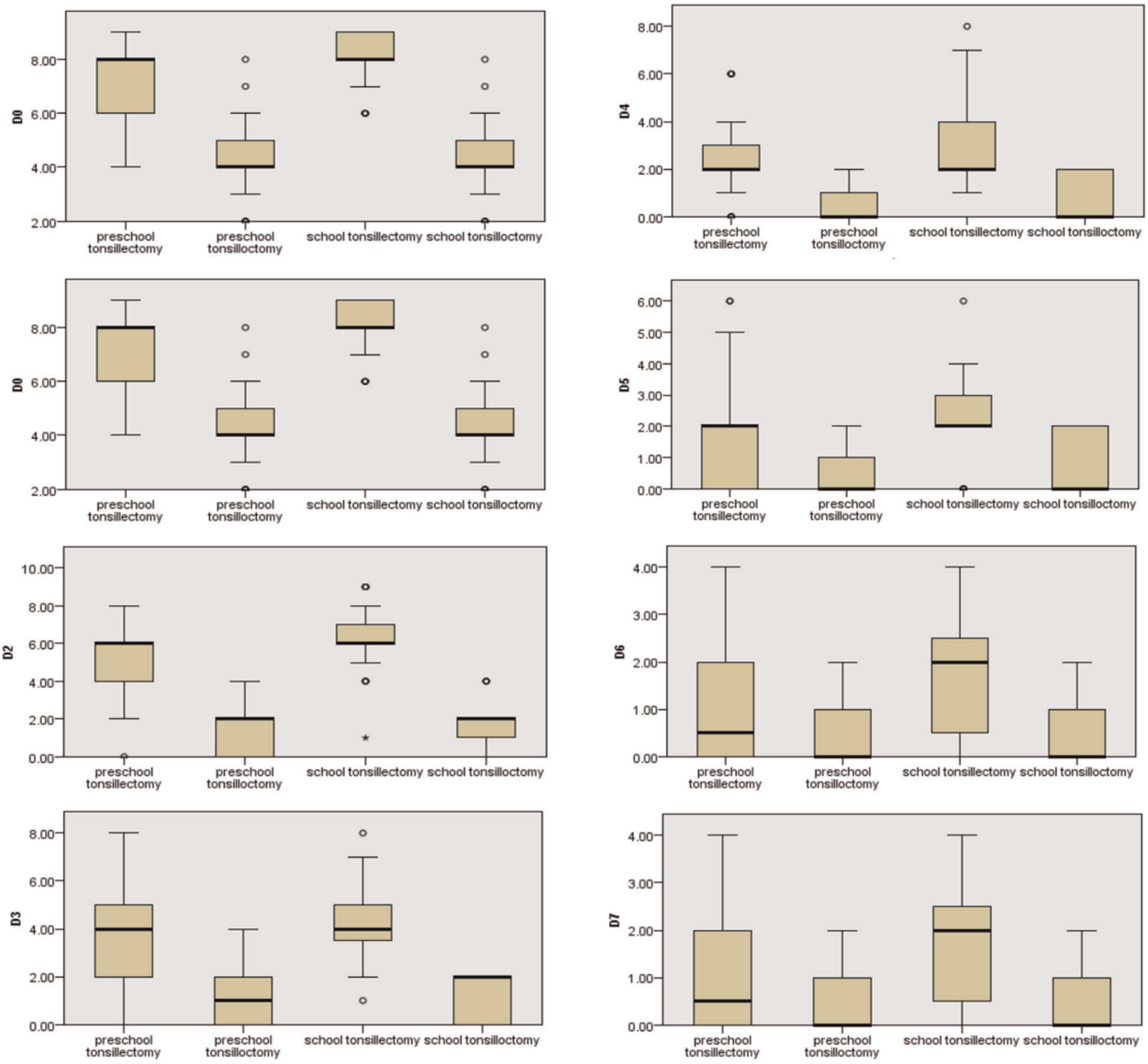

FIGURE 1
The comparison of pharyngeal pain (PPPM scores) among preschool-age tonsillotomy, preschool-age tonsilletomy, school-age tonsillotomy, and school-age tonsilletomy from D0~D7.

the postoperative pain of children undergoing surgery. Age is an important factor affecting preoperative anxiety in children, as it is related to their responses to the outside world (15). Preoperative parental comfort can effectively relieve preoperative anxiety in preschool children. On the other hand, informing school-age children undergoing total tonsillectomy about the degree and duration of postoperative pain may aggravate their preoperative anxiety and lead to severe postoperative pain.

Pain assessments in children have been based mostly on the visual analog scale. However, a previous study found that the PPPM correlated well with pain (16), and another study recommended its use for family assessments of pain after pediatric surgeries (17). In this study, we used the PPPM to observe postoperative behavioral changes in children. Sakki et al. (18) reported that both patients undergoing tonsillotomy and patients undergoing tonsillectomy lost weight postoperatively, with weight loss in the first week being greater among the latter. Our results are consistent with these findings. Weight loss may be related to the relevant dietary recommendations of the Clinical Practice Guidelines for Standardized Low-Temperature Plasma Radiofrequency Ablation Tonsillectomy and Adenoidectomy in Children (19) for partial or total tonsillectomy. About three weeks after the

operation, the patient can return to a normal diet, depending on the wound's condition. Weight loss in the tonsillectomy group in this study was associated with insufficient food intake due to pain. In the tonsillotomy group, although the patients experienced mild postoperative pain, they also lost weight because their diet was restricted and changed.

In this study, compared to tonsillectomy, tonsillotomy was associated with less postoperative pain, which lasted for a shorter time, less weight loss, and faster recovery than tonsillectomy. Tonsillotomy reflects our enhanced recovery after surgery practice, which improves the treatment effects, reduces postoperative complications, and accelerates postoperative recovery, thereby shortening hospitalization times and reducing medical costs (20).

Compared with previous studies, ours is a prospective study, including 121 patients, that reduced the effect of bias. Previous studies have mostly used VAS or Wong–Baker FACES score, while we used PPPM score, which is related to pain. This approach resulted in a better correlation. In our study, we subgrouped patients according to age and analyzed the differences in pain patterns between the postoperative day 0 and postoperative day 7, the partial and total tonsillectomy groups, and the two age groups. Moreover, we observed swelling of the pharynx from the first to the seventh postoperative day in the partial and total tonsillectomy groups, which better explained the pain degree of the two groups of patients. This study has certain limitations. First, the sample size was small. Second, factors such as anxiety and differences in families' educational levels that may have affected the results were not considered.

In conclusion, the pain caused by tonsillotomy in children with OSA was obvious over the first 24 h after the operation and subsequently mild over the first postoperative week. The pain levels, pharyngeal swelling and weight loss associated with tonsillotomy were lower than those associated with tonsillectomy. On the fifth, sixth, and seventh postoperative days, compared with preschool children, tonsillotomy in school-age children is more advantageous in school-age children.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Zhengzhou Central Hospital Affiliated to Zhengzhou University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

YD designed this clinical trial and wrote the primary article; YD gave guidance on experimental design and thesis writing; LT, SX and HW participated in data statistics; JZ and WH gave advices to this trail and English writing. All authors contributed to the article and approved the submitted version.

Conflict of interest

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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Long term NIV in an infant with Hallermann-Streiff syndrome: A case report and overview of respiratory morbidity

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Hallermann-Streiff syndrome (HSS) is a rare congenital syndrome with different anomalies including midface hypoplasia, beak nose and micrognathia. The upper airways narrowness can lead to severe respiratory complications such as obstructive sleep apnoea syndrome (OSAS), particularly in infancy. The management of these severe OSAS is difficult and poorly documented in literature. We report the case of an infant with HSS complicated by severe and early OSAS successfully managed with non-invasive ventilation (NIV), provide an overview of respiratory morbidities and discuss treatment options for HSS-related OSAS.

KEYWORDS
Hallermann-Streiff syndrome, NIV (non-invasive ventilation), OSAS (Obstructive sleep apnea syndrome), infant, success

Introduction

Hallermann-Streiff syndrome (HSS) is a rare congenital syndrome, first described by Francois in 1948 (1). To date, less than 200 individuals with a HSS have been described worldwide (2). A recent publication estimated its prevalence at 1/10 million in Japan (3). The phenotype is highly recognizable but genetic basis and molecular defect remain unknown (4). It is defined by the association of dyscephaly with midface hypoplasia, beak shape nose and micrognathia, proportional short stature, hypotrichosis, skin atrophy, dental abnormalities, microphthalmia, bilateral congenital cataracts and inconstant neurodevelopmental delay. Respiratory disorders are a major issue, especially during childhood. The upper airways narrowness leads to obstructive apneas, anesthetic management difficulties and potentially life-threatening events in severe cases (5). Obstructive Sleep Apnea Syndrome (OSAS) management in HSS is not well established and tracheostomy remains the chosen option when severe obstruction occurs (4). However, since last decades we face an important increase of non-invasive ventilation (NIV) use in children in several indications including OSAS related to facial anomalies (6).

We report the case of an infant with HSS complicated by severe and early OSAS, successfully managed with NIV. Furthermore, we give an overview of respiratory morbidities and discuss therapeutic options in OSAS related to HSS.

Case

A female infant was born after 38 weeks of gestation of a normal pregnancy with birth parameters of 3110 g for the weight (percentile 25–50), length of 47 cm (percentile 5) and cranial circumference of 32.5 cm (percentile 5). She showed facial dysmorphic signs: tiny nose with marked nasal cartilage hypoplasia and skin atrophy, micro-retrognathy, microcephaly, neonatal teeth (51, 61, 71 and 81), bilateral congenital cataract, atrial septal defect and two small apical ventricular septal defects. HSS was strongly suspected, based on typical clinical phenotype. Genetic analyses (Next Generation Sequencing – NGS - of whole exome with analysis of 82 genes involved in early ageing and 1,832 genes involved in developmental disorders) were not able to find any causative genetic anomaly. First evaluation by Ear Nose and Throat (ENT) specialist through upper airways endoscopy at day 3 revealed narrow but permeable choanas without associated laryngo- trachea-malacia nor adenotonsillar hypertrophy. She was referred to pediatric pulmonologist because of high risk of apneas in this syndrome. First nocturnal oxymetry at day 4 and second at 5 months were normal. Successive peadiatric evaluations revealed a neurodevelopmental delay and a failure to thrive related to multifactorial feeding difficulties with inadequate intakes, daily aspirations and severe gastroesophageal reflux. At 8 months, she was admitted in hospital for investigations. She had an axial hypotonia (difficult head hold, no sitting) but a good grasp of objects and a good interaction despite the visual impairment. During the hospital stay, apneas were observed and the polygraphy confirmed a severe OSAS with an obstructive apnea-hypopnea index (OAHI) of 25/h and 0.4% of nighttime with SpO2 < 90%. Repeated venous blood gas showed no hypercapnia nor bicarbonate elevation. ENT endoscopy was repeated, showing still narrow choanas and adenoid hypertrophy, driving to adenoidectomy. At the same time, surgical gastrostomy, without anti-reflux surgery, was performed for enteral feeding considering the low weight (3,870 g, < 3 percentile).

Six weeks later, snoring and disrupted sleep persisted when the polygraphy showed worsening of OSAS, with an OAHI of 140/h, and 41% of nighttime with SpO2 < 90% (**Figure 1A**). Because of the severe hypoplasia of face middle third, tracheostomy was suggested to treat this severe OSAS. After multidisciplinary discussions involving the parents, ENT and maxillofacial surgeons, intensivists, pulmonologists and physiotherapists, we first chose to try NIV therapy.

Nighttime NIV therapy was therefore initiated at 10-months-old (4,450 g/59,5 cm) in an intermediate care unit. Continuous positive airway pressure (CPAP) with a nasal mask was first started. Tolerance of CPAP was good but the polygraphy under CPAP showed no improvement of the OSAS. Increasing the level of Expiratory Positive Airway Pressure (EPAP) led to poor tolerance during expiratory time due to high level of pressure limiting expiratory flow and no additional gain on obstruction of the inspiratory flow. Therefore, we tried spontaneous bilevel positive pressure support (BPAP), using a Trilogy 100© (Philips Respironics, Pennsylvania, USA) with single limb circuit and a nasal mask Respireo SOFT Baby© (AirLiquide, France). EPAP and Inspiratory Positive Airway Pressure (IPAP) were subsequently modified to optimize inspiratory and expiratory flows as well as tolerance of NIV therapy and clinical respiratory pattern. After this titration phase, EPAP and IPAP were + 5 and + 9 cmH2O, respectively. Due to the risk of aspiration, enteral feeding was exclusively performed during daytime, with no overlap with NIV. Polygraphy under NIV, after 5 days of BPAP support, showed dramatic improvement of OSAS with an obstructive AHI of 7.6/h and only 1% of time with SpO2 < 90% (**Figure 1B**).

After training the parents regarding NIV and gastrostomy management, the patient was discharged at home. Respiratory situation remained good during the following year without any adverse event. The median time of respiratory support was 8 h overnight and no additional modification of NIV parameters was needed. Regular maxilla-facial evaluations showed no NIV-induced facial deformation. Parents reported rapid improvement in psychomotor acquisitions, interaction and general behavior.

One year later, polygraphy under NIV remained normal, with an OAHI of 1.4/h and less than 1% of time with SpO2 < 90%. To date, at 2 years old, the neuro-development was estimated equivalent to a 12-month-old child. Regular evaluations were made by a maxillo-facial surgeon. Facial evolution was as good as expected, with no clinical evidence of negative consequence of the nasal mask pressure on midface development.

Figure 2 displays photos of the patient with and without NIV.

Discussion

Respiratory morbidity is important in HSS. It is highly variable but may potentially be life-threatening (7–10). Microretrognatia, microstome, and mid-face hypoplasia with narrow nose, sometimes associated with glossoptosis or laryngomalacia, result in an important narrowness of upper airways leading to anesthetic airway management difficulties (11) and OSAS (2). Tracheomalacia has also been reported in

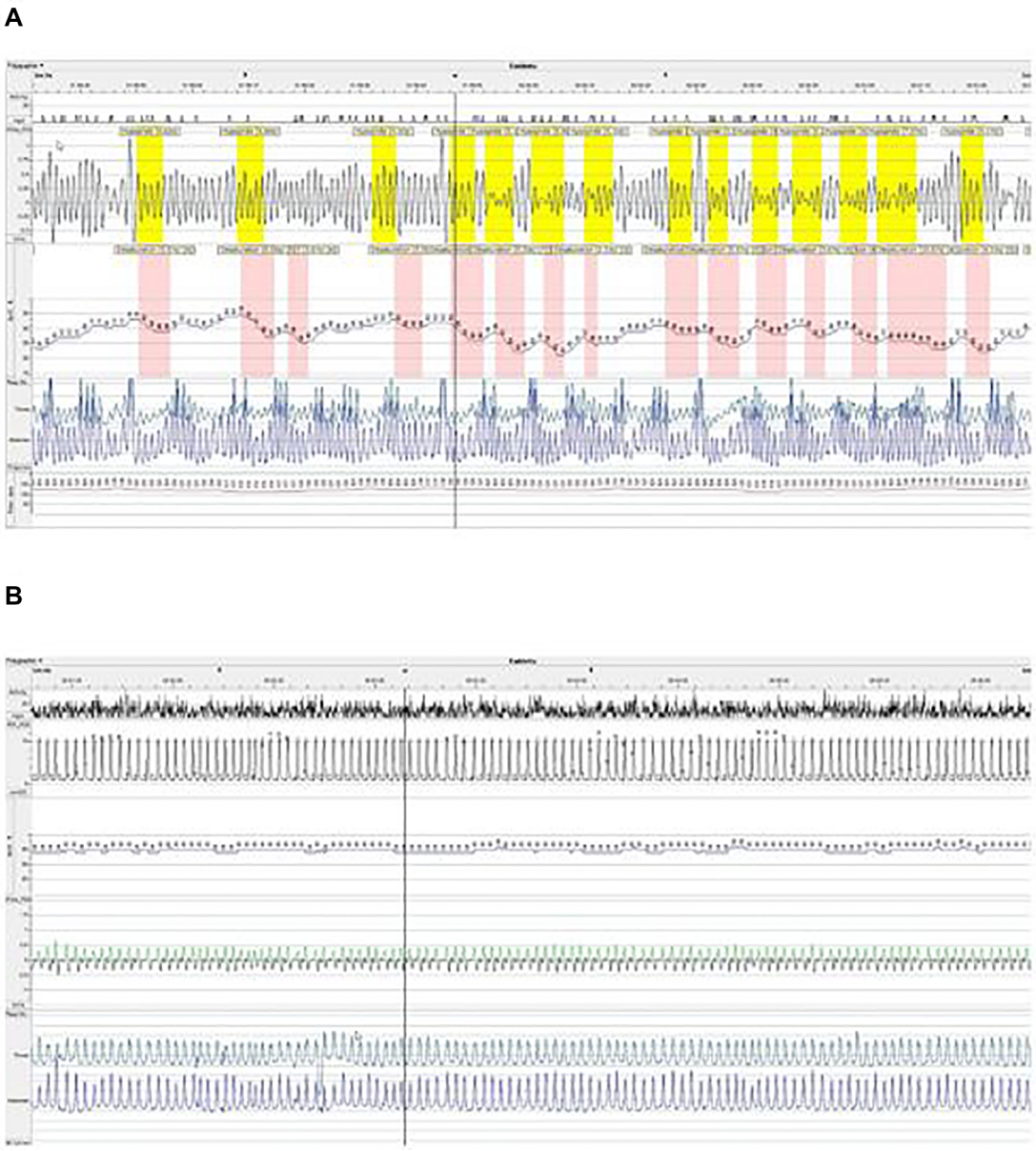

FIGURE 1
Polygraphy after adenotonsillectomy without NIV treatment (A) and under NIV treatment (B) in (A,B), we show extracts from polygraph plot with nasal flux (XFlow), oxygen saturation (SpO2), thoracic and abdominal movements and cardiac pulse. In (A), we see an obstructive breathing pattern with frequent hypopneas characterized by a drop of airflow associated with desaturations ≥3% of oxygen. In (B), under NIV, we see a regular breathing pattern with a complete disappearance of obstructive events and desaturation.

some cases of HSS (9), and tracheobronchoscopy should be performed in case of suggestive symptoms (early-onset inspiro-expiratory noise, fixed wheeze, recurrent infections, or chronic brassy cough). No published data or expert opinion supports that tracheomalacia management should be different in the context of HSS than in other conditions (12).

OSAS is definitely the main respiratory issue in HSS, but is challenging as no specific guidelines for OSAS screening and management in HSS is available. Therefore, physicians have to refer to general guidelines for OSAS in children (13, 14) or to experiences and expert recommendations in other craniofacial malformations (6, 15). Prevalence of OSAS in HSS is unknown, but may be high as reported in about half of the published cases. As in other craniofacial malformations, OSAS severity is highly variable between patients and is diagnosed at different ages (6), depending on the severity of facial anomalies and the possible association with other individual characteristics not related with HSS and influencing upper

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FIGURE 2
Current front and profile photography, with and without NIV.

airways obstruction such as adenotonsillar hypertrophy or overweight. Regarding our patient, OSAS appeared during the first months of life (confirmed at 8 months) but in other HSS cases, OSAS was diagnosed later in childhood, even at

adulthood (16). In syndromic cranio-synostosis such as Alpert or Crouzon syndrome, authors described an improvement of OSAS severity with growth (17), but no equivalent data are available in HSS.

In our case, severe OSAS was diagnosed at 8 months old by a polygraphy, when previous evaluations were normal, and therefore reassuring, but only based on nocturnal oxymetry. A rapid worsening of OSAS during the first months of life is possible, especially considering the role of adenoid growth in its physiopathology, but we can legitimately ask ourselves if the oxymetries did not underestimate apneas. Based on this experience, even if oximetry is more and more used for OSAS evaluation (18), we would recommend polygraphy [with measurement of nasal flow, thoracic and abdominal movements, heart rate and transcutaneous oxymetry (19)] for OSAS screening in babies with craniofacial malformations, to be able to detect OSAS as early as possible. The choice between polygraphy and polysomnography for OSAS evaluation can also be discussed. Even if the current gold standard for OSAS diagnostic in children remains polysomnography, it is now established in literature that polygraphy, because of its better accessibility and better feasibility especially for infants, is a good alternative to polysomnography for OSAS diagnosis (13).

Pediatric OSAS often requires a multidisciplinary management, especially in case of craniofacial malformations, including HSS. In children with craniofacial malformations, such as in all children, adenotonsillectomy must be provided in case of obstructive adenotonsillar hypertrophy, as we did for our patient (13). Unfortunately in this case, OSAS persisted after this first surgical step. There is no available data on adenotonsillectomy efficacy for OSAS treatment in HSS but it is widely reported in other craniofacial malformations that OSAS can persist after adenotonsillectomy, especially if initial OSAS was severe (6, 13). Therefore, following ERS recommendations for OSAS management in children (13), an assessment by polysomnography or polygraphy should be systematically performed after adenotonsillectomy in HSS population.

If adenotonsillectomy is not indicated or in case of persistent severe OSAS after adenotonsillectomy, the second line of treatment must be carefully discussed in a multidisciplinary team. In our case, regarding the severity of OSAS, the potential negative impact on growth and neurodevelopmental status and the high risk of life-threatening obstructive event, an additional treatment with short-term efficacy was mandatory. Maxillofacial surgery, tracheostomy and non-invasive positive pressure support are the three main therapeutic options to discuss in order to find the personalized most appropriate strategy.

- *Maxillo-facial surgery*: Several surgical options have been proposed for HSS, depending on the severity and location of the middle third hypoplasia (20, 21). These surgical treatments appear to be efficient for OSAS treatment, knowing that reconstructive surgery are usually proposed at an adult's age or in late adolescence, as midface advancement required a mature facial ossification. In case of severe obstruction early in life, as experienced by our patient, it was not considered as a short-term option.
- *Tracheotomy:* Several cases of HSS undergoing tracheostomy have been reported, with resolution of the OSAS (8). This is the most radical option to bypass upper airway obstruction, and the chosen treatment in main of the published cases with HSS-related OSAS. This option should be considered after careful evaluation considering the consequences on orality, speech development and sociability, and the potential risk of complications (infectious complications, long-term tracheal stenosis or granulation, life-threatening decannulation or cannula obstruction events).
- *Non-Invasive Ventilation (NIV) therapy:* NIV (including–CPAP and–BPAP) is a validated treatment of OSAS in children if ENT and/or maxillofacial surgical options are impossible or ineffective (13). To our knowledge, there is no published case of HSS children with severe OSAS treated by NIV to date, but in other craniofacial malformations, it is now a well-established therapeutic option (6), with good efficiency on OSAS and good tolerance. However, some difficulties should be mentioned. First, finding an appropriate interface can be challenging because of the paucity of available masks suitable for young children. This is even more challenging in HSS babies given their specific facial features. Second, the risk of broncho-inhalation in case of reflux or vomiting should also be evaluated, especially in young children. Third, the impact of mask pressure on the face development has to be discussed and monitored if used for a long time. Finally, depending of the severity of the obstruction, high pressure level could be required which can be poorly tolerated by the child.

In our case, the risk of NIV intolerance was relatively high, considering the severe midface hypoplasia which reduce the choice of appropriate interface, the narrowing of airways at different stages (i.e., nares-choanas-oropharyngeal), the severe gastro-oesophageal reflux with risk of aspiration, and the small weight with possible ventilation asynchronism. Despite this, we decided to try NIV therapy for our patient, which was considered by the team and parents as the less invasive and the more appropriate option.

So far both the parents and the multidisciplinary medical team remain convinced that NIV was the good therapeutical choice for this child. NIV corrected OSAS, helped the patient to grow and to continue her neurodevelopmental progress, being the bridge to

maxillofacial - hopefully curative—surgery in several years and avoiding the need of tracheostomy.

In our opinion, the success of NIV in this case was multifactorial. The multidisciplinary approach, including paediatric pulmonology, intensive care and ENT specialists, maxillo-facial surgeon, physiotherapist, and a well-experienced team in NIV in children with access to appropriate devices, allowed a careful and global evaluation of the feasibility and a fine tuning of the NIV device. Nevertheless, the success of NIV in such cases would not be possible without very motivated and appropriate parents. Obviously, close follow-up is mandatory during NIV therapy in order to detect any NIV adverse event, to evaluate adequacy of NIV support and OSAS evolution, performing iterative polygraphy, which we believe should be performed at least once a year during NIV treatment. In this context of facial congenital malformation, regular evaluations by maxillo-facial surgeon are mandatory to properly assess NIV impact on mid-face growth.

This success well illustrates that NIV should be considered in patients with HSS and OSAS, such as in other craniofacial malformations like Treacher Collins, Pierre-Robin or Alpert Syndrome.

Conclusion

OSAS is the main respiratory issue in HSS, mainly due to facial malformations. Screening for OSAS should be systematic within the first months of life and repeated during childhood, preferably by polygraphy or polysomnography. NIV could be considered as a safe and feasible option for OSAS treatment, as an alternative to early tracheostomy, in addition or as a bridge to ENT and/or maxillofacial surgery.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Ethics statement

Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

SG: drafting the work, substantial contributions to the conception or design of the work. SB: substantial contributions to the conception or design of the work, revising it critically for important intellectual content. QDH: substantial contributions to the conception or design of the work, revising it critically for important intellectual content. VB: substantial contributions to the conception or design of the work, revising it critically for important intellectual content. TF: substantial contributions to the conception or design of the work, revising it critically for important intellectual content. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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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Relationship between serum brain-derived neurotrophic factor and cognitive impairment in children with sleep-disordered breathing

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Background: As an important neuroprotective factor, the brain-derived neurotrophic factor (BDNF) may have a key role in cognitive impairment in children with sleep-disordered breathing (SDB). The main aim of this study was to compare the levels of BDNF and tyrosine kinase receptor B (TrkB) in normal children and those with obstructive sleep apnea (OSA) and primary snoring (PS) and to explore a possible link between BDNF/TrkB, inflammation, and SDB with cognitive impairment in children.
Methods: A total of 44 OSA children and 35 PS children who completed polysomnography between October 2017 and October 2019 were enrolled. At the same time, 40 healthy children during the same period were included as a control. Enzyme-linked immunosorbent assay was used to measure serum indices of BDNF, TrkB, interleukin-1beta (IL-1β), and tumor necrosis factor-alpha (TNF-α). Correlation and pooled analyses were performed between the cognitive scores and four serological indicators. Logistic regression was used to analyze the risk factors for cognitive impairment.
Results: Significant differences were found in serum BDNF, TrkB, IL-1β, and TNF-α between the three groups (all $P < 0.01$). The serum BDNF and TrkB in the OSA and PS groups were lower than those in the control group, whereas the serum IL-1β and TNF-α were higher than those in the control group (all $P < 0.05$). Moreover, among these four indices, the strongest correlation was found between BDNF and the Chinese Wechsler Intelligence Scale (all $P < 0.05$). Logistic regression analysis revealed a correlation between OSA status, TrkB, and course of mouth breathing and cognitive status.
Conclusion: The levels of serum BDNF and TrkB were related to cognitive impairment in children with SDB. Also, BDNF and TrkB could be used as noninvasive and objective candidate markers and predictive indices of cognitive impairment in children with SDB.

KEYWORDS
sleep-disordered breathing, BDNF, trkB, cognitive impairment, pediatric

Introduction

Sleep-disordered breathing (SDB) is a highly prevalent disease characterized by abnormalities in respiratory patterns, which cause arousals and affect the quantity of ventilation or arterial oxygen saturation (SaO_2) during sleep, and it is characterized by intermittent hypoxia and sleep fragmentation. SDB is described as a spectrum of disorders from primary snoring (PS) to obstructive sleep apnea (OSA) on the basis of apnea indices from polysomnography (PSG) (1). According to the meta-analysis study of SDB in children, the prevalence of OSA ranged between 1% and 4%, and the prevalence of PS was as high as 7.45% (2). Nocturnal intermittent hypoxia and fragmented sleep caused by SDB can lead to adverse health consequences such as cognitive impairment (3). Regrettably, the research on the impact of SDB (including PS and OSA) on cognitive impairment in children was more focused on clinical research, with relatively few molecular mechanism studies compared with that on adults. Moreover, the assessment of cognitive impairment in children is usually performed using various scales, which may lead to subjective results. In this context, the exploration of objective and easily measurable biomarkers is of great importance in clinical practice.

Brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family, is widely expressed in various brain regions. BDNF can pass through the blood–brain barrier, and its concentration in brain tissue and blood is closely related (4). Tyrosine kinase receptor B (TrkB) is a specific receptor for BDNF, and BDNF/TrkB signaling pathway has an important protective role in neuronal injury. Reduced BDNF levels in the human brain are associated with cognitive impairment caused by neurodegenerative diseases, such as Alzheimer's disease and Parkinson's schizophrenia (5, 6). In addition, Xie et al. used a mouse model of chronic intermittent hypoxia (IH) to provide convincing evidence for the key role of BDNF in OSA-induced cognitive impairment. They found that the expression of BDNF was significantly reduced after chronic IH in mouse. Also, supplementation of BDNF could rescue and prevent IH-induced long-term potentiation deficits (7, 8). SDB can induce a local and systemic inflammatory response, leading to the upregulation of inflammatory cytokines (9, 10), such as interleukin-1beta (IL-1β) and tumor necrosis factor-alpha (TNF-α), which could increase the permeability of the blood–brain barrier and lead to neuroinflammation or neurodegeneration with a consequent cognitive impairment (11–14). However, no clinical studies are confirming the relationship between BDNF and cognitive impairment in children with SDB, nor relevant research about detailed stratified analyses of PS and OSA in children.

It is now generally accepted that OSA is associated with cognitive and behavioral dysfunction in children (15, 16). Yet, the growing evidence showed that PS, the mildest and most common form of SDB, is not benign but carries a similar risk for cognitive and behavioral impairment as OSA in children (17). A review of the literature suggests, however, that the expression of serum BDNF and TrkB in PS children and their differences with OSA children have not been fully exploited. This study aimed to (1) investigate whether there are differences in the serum levels of BDNF and TrkB in OSA children, PS children, and healthy children, and (2) explore a possible link between BDNF/TrkB, inflammation, and SDB with cognitive impairment.

Methods

Study design and subjects

This cross-sectional observational study included 44 OSA children and 35 PS children diagnosed by PSG examination who were admitted to the Department of Otorhinolaryngology—Head and Neck Surgery of the Second Affiliated Hospital of Xi'an Jiaotong University between October 2017 and October 2019 because of habitual snoring during sleep. At the same time, 40 healthy children were recruited from the Children's Health Center of the same hospital as the control group. Inclusion and exclusion criteria are described in detail in the Supplementary Materials.

This study was approved by the ethics committee of the Second Affiliated Hospital of Xi'an Jiaotong University (approval no. 2017058). All children who participated in the research were accompanied by parents, who signed informed consent. The inspection items and processes involved in this study are in line with the declaration of Helsinki.

Subject characteristics

All subjects underwent a routine medical history and physical examination by otolaryngologists, oral and maxillofacial surgeons, pediatricians, and child psychiatrists to assess comorbidities. In addition, gender, age, course of snoring, course of mouth breathing, course of chocking, paternal education level, maternal education level, body mass index (BMI), tonsil size, adenoidal/nasopharyngeal ratio, and Epworth Sleepiness Scale were recorded. Tonsil size was assessed using the Brodsky standardized system (18).

PSG is considered to be the gold standard for the diagnosis of SDB. All children who presented with habitual snoring underwent an overnight PSG assessment, during which relevant PSG data were collected, including apnea-hypopnea index, obstructive apnea index, obstructive apnea-hypopnea index (OAHI), rapid eye movement-respiratory disturbance index (REM-RDI), non-rapid eye movement-respiratory

disturbance index (NREM-RDI), average SaO_2, minimum SaO_2, sleep efficiency, respiratory arousal index, REM respiratory arousal index, NREM respiratory arousal index. The obtained PSG data were scored according to the American Academy of Sleep Medicine guidelines (19). All subjects were grouped into PS and OSA groups according to OAHI. Also, OAHI was defined as the total number of obstructive apneas, mixed apneas, and obstructive hypopneas per hour of total sleep time. PSG data were evaluated and analyzed by two trained technicians, and were then reviewed by sleep specialists. Additionally, OSA diagnosis was based on OAHI ≥ 1 event per hour during PSG. PS was diagnosed in children with habitual snoring and OAHI < 1 event per hour (20).

Measurement of serum indicators

The venous blood samples were drawn with a serum separator tube from all subjects in the morning between 6:30 AM and 7:00 AM and were centrifuged at $1,900 \times g$ for 10 min to separate the upper serum, which was then stored at −80°C for subsequent use. Moreover, serum levels of BDNF (#RAB0026, Sigma-Aldrich), TrkB (#orb381119, Biorbyt), IL-1β (#QLB00B, R&D Systems), and TNF-α (#QTA00C, R&D Systems) were determined by enzyme-linked immunosorbent assay. Finally, the measurement of each sample was repeated three times, and the data were reported as the average of the three measurements. The inter-assay coefficient of BDNF, TrkB, IL-1β, and TNF-α was 3.6%, 4.0%, 3.4%, and 3.6%, respectively, and the intra-assay coefficient was 4.3%, 5.1%, 4.4%, and 4.1%, respectively.

Behavioral and cognitive assessment

The Chinese Wechsler Intelligence Scale (C-WISC) and Conners' Parent Rating Scale (CPRS) were used to assess cognitive and behavioral function. The Wechsler Intelligence Sale (WISC) has three intelligence quotient (IQ) domains: verbal intelligence quotient (VIQ), performance intelligence quotient (PIQ), and full intelligence quotient (FIQ). C-WISC has been revised from the WISC for Children based on the Chinese cultural background, and FIQ < 90 means abnormal intelligence (21, 22). CPRS is a questionnaire designed for parents to assess their children's behavioral problems (23). Assessments were performed by two clinical psychologists who were blind to the subjects' clinical data.

Statistical analysis

SPSS 21.0 (IBM Corporation, Armonk, NY, USA) and GraphPad Prism 7 (GraphPad Software Inc., San Diego, CA, USA) were used for data analysis. Descriptive characteristics across groups were compared using Chi square test or Fisher's exact test for categorical variables and nonparametric rank-sum test for grade data, and analysis of variance or for continuous variables. Continuous variables were tested for normality using the Shapiro–Wilk test, and the data with normal distribution were compared by analysis of variance or student's t test. Data with non-normal distribution were tested by nonparametric test. The relationships between continuous variables were explored using Pearson's correlation or Spearman's correlation.

A logistic regression model was used to assess the factors influencing the cognitive status. Logistic regression analysis was performed using intellectual status as the dependent variable (FIQ ≥ 90 indicates normal intelligence, FIQ < 90 indicates abnormal intelligence), and paternal education level, maternal education level, OSA status, course of snoring, course of choking, course of mouth breathing, Epworth Sleepiness Scale, gender, age, BMI, BMI-Z score, conduct problem, learning problem, somatic complaints, hyperactive, Conners' index of hyperactivity (CIH), anxiety, BDNF, TrkB, IL-1β and TNF-α as the independent variables were used for initially screening by using the least absolute shrinkage and selection operator of the independent variables. Further, the screened variables were included in logistic regression, adjusting for possible confounding factors such as age, sex, BMI-Z score. $P < 0.05$ was considered to be statistically significant.

Results

Subject characteristics

The patient flow in the current study is described in detail in **Figure 1**. After the inclusion and exclusion criteria were applied, this dataset included 119 children, with 44 children in the OSA group, 35 children in the PS group, and 40 healthy children in the control group.

The demographic and clinical characteristics of the groups are summarized in **Table 1**. There were no significant differences in age, BMI, BMI-Z score, and paternal education level among the three groups; however, there were statistically significant differences in gender ($P < 0.05$) and maternal education level ($P < 0.05$). In addition, there were no significant differences in other baseline data, including the course of snoring, course of mouth breathing, course of chocking, adenoidal/nasopharyngeal ratio, Epworth Sleepiness Scale, and tonsil size between the OSA group and the PS group.

The PSG results of OSA group and PS group are shown in **Table 2**. As expected, most of PSG parameters were significantly different between the two groups ($P < 0.0001$), except for sleep efficiency.

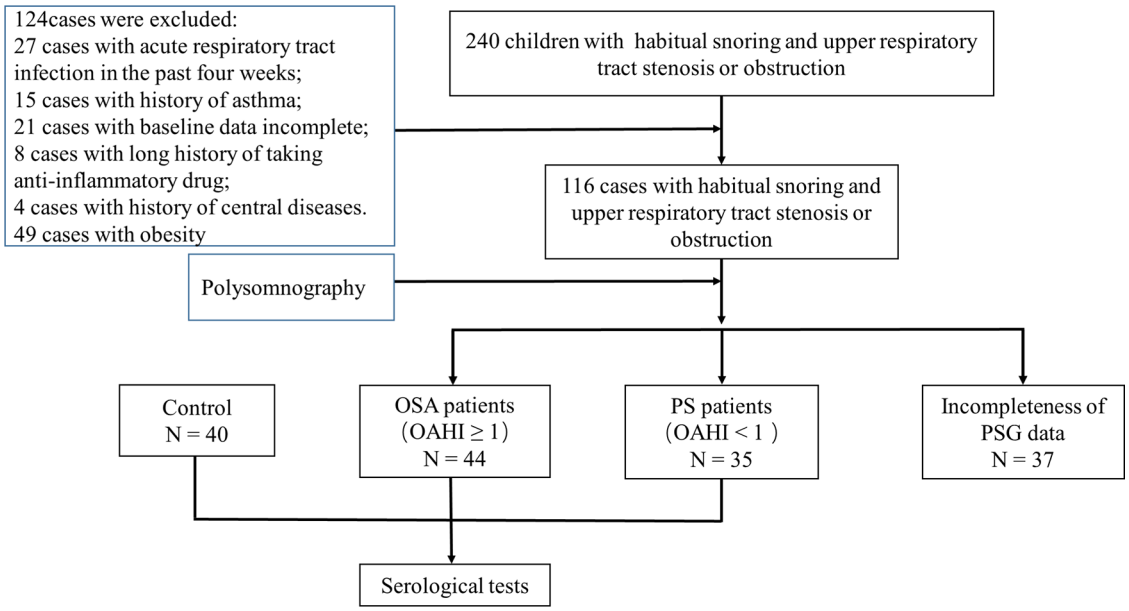

FIGURE 1
Summary of subject inclusion.

Serum indicators, behavioral and cognitive assessment

The differences in cognitive and behavioral scores between groups are shown in **Table 3**. In the CPRS, a comparison among the three types of children showed significant differences in learning problems and hyperactivity; however, there was no significant difference in the other four indices in the three groups. Additionally, compared with the patients in the PS group, the patients in the OSA group had significantly lower FIQ, VIQ, and PIQ (all $P < 0.05$).

The serum levels of BDNF and TrkB in OSA and PS children were significantly lower than those of the control group (all $P < 0.05$), especially in the OSA group. Furthermore, there were also significant differences in IL-1β and TNF-α among the three groups ($P < 0.001$), with a significant increase in the OSA and PS groups (**Table 4**; **Figure 2**).

Correlation analysis

Correlation analysis showed a good correlation between BDNF and TrkB ($r = 0.919$, $P < 0.01$), IL-1β ($r = -0.312$, $P < 0.01$) and TNF-α ($r = -0.507$, $P < 0.01$). Besides, there was also a correlation between BDNF and OAHI ($r = -0.315$, $P < 0.01$), and it was worth noting that there was a correlation between BDNF and NREM−RDI rather than REM−RDI ($r = -0.356$, $P < 0.01$). In CPRS, only hyperactivity was correlated with BDNF ($r = -0.241$, $P < 0.01$). In C-WISC, the Pearson correlation, which was carried out for VIQ, PIQ, FIQ, and BDNF, revealed a positive correlation (VIQ: $r = 0.317$, $P < 0.01$; PIQ: $r = 0.300$, $P < 0.01$; FIQ: $r = 0.249$, $P < 0.05$). Furthermore, the positive correlation was also observed between TrkB and FIQ ($r = 0.316$, $P < 0.01$), and PIQ ($r = 0.307$, $P < 0.01$) (**Table 5**).

Additionally, a negative correlation was found between TNF-α and VIQ ($r = -0.246$, $P < 0.05$) and PIQ ($r = -0.272$, $P < 0.05$), whereas no correlation was found between IL-1β and PIQ, VIQ, or FIQ (**Figure 3**).

Analysis of factors influencing the cognitive status in subjects

As evident from **Table 6**. The results showed the association of OSA status, course of mouth breathing and TrkB with intellectual status. Specifically, in analyses adjusted for age, sex and BMI-Z score, OSA children had a higher risk of cognitive impairment than those with an OAHI < 1 [odds ratio (OR) = 4.582, 95% confidence interval (CI): 1.496 to 14.034], and beneficiaries who with high levels of TrkB had a significantly lower odds of developing cognitive impairment (OR = 0.362, 95% CI: 0.157 to 0.836). Additionally, the longer duration of mouth breathing also increases the risk of cognitive impairment (OR = 1.043, 95% CI: 1.010 to 1.077).

TABLE 1 Comparisons of demographic and clinical characteristics among three groups.

	All	OSA patients	PS patients	control	*P*
Gender (male/female, *n*)[a]	119 (72/47)	44 (34/10)	35 (18/17)	40 (20/20)	<0.05
Age (year)[b]	6.97 ± 2.01	6.66 ± 1.96	7.43 ± 2.22	6.90 ± 1.83	0.234
Course of snoring (months)[c]	24.0 (8.0-36.0)	24.0 (12.0-36.0)	24.0 (5.0-36.0)	0.0 (0.0-0.0)	0.512
Course of mouth breathing (months)[c]	12.0 (5.0-24.0)	12.0 (5.3-24.0)	24.0 (5.0-36.0)	0.0 (0.0-0.0)	0.232
Course of choking (months)[c]	2.0 (0.0-12.0)	3.0 (0.0-12.0)	0.0 (0.0-6.0)	0.0 (0.0-0.0)	0.077
Epworth Sleepiness Scale[c]	4.0 (2.0-6.0)	4.0 (2.0-6.0)	4.0 (2.0-6.0)	N/A	0.568
BMI (kg/m^2)[b]	16.44 ± 2.64	16.70 ± 2.95	16.37 ± 2.53	16.22 ± 2.39	0.699
BMI-Z score[b]	0.21 ± 1.26	0.30 ± 1.29	0.10 ± 1.07	0.21 ± 1.39	0.782
adenoidal/nasopharyngeal ratio[d]	0.68 ± 0.10	0.68 ± 0.10	0.67 ± 0.11	N/A	0.493
Paternal education level[c]					0.168
0	0	0	0	0	
1	5	1	2	2	
2	15	11	2	2	
3	20	8	6	6	
4	33	10	11	12	
5	40	12	12	16	
6	6	2	2	2	
Maternal education level[c]					<0.05
0	1	1	0	0	
1	4	0	2	2	
2	20	14	4	2	
3	20	9	5	6	
4	25	8	7	10	
5	44	11	15	18	
6	5	1	2	2	
Tonsil size (*n*)[c]					0.060
0	3	0	3	N/A	
1	3	2	1	N/A	
2	31	14	17	N/A	
3	6	5	1	N/A	
4	36	23	13	N/A	

BMI, body mass index; The education level: 0, without education; 1, completed primary school; 2, completed part secondary education; 3, completed secondary education; 4, completed postsecondary training; 5, completed an undergraduate university degree; 6, completed a postgraduate university degree; OSA,: obstructive sleep apnea; PS, primary snoring.

[a]Chi-squared test or Fisher's exact test.

[b]Analysis of variance test.

[c]Nonparametric test.

[d]The student's *t* test.

TABLE 2 Comparisons of PSG characteristics of the OSA and PS patients.

	All	OSA patients	PS patients	*P*
AHI (events/h)	6.14(0.70–12.00)	8.99(6.78-18.54)	0.70(0.30–0.90)	<0.0001
OAI (events/h)	0.69 (0.10–2.50)	2.20 (1.30–4.00)	0.10 (0.00–0.30)	<0.0001
OAHI (events/h)	2.90(0.30–7.40)	6.81(4.49–14.67)	0.20(0.10–0.40)	<0.0001
REM-RDI (events/h)	7.20 (1.10–14.07)	13.19 (8.95–30.63)	0.70 (0.50–1.89)	<0.0001
NREM-RDI (events/h)	5.09(0.70–10.29)	8.54 (5.41–15.41)	0.65(0.20–0.89)	<0.0001
Average SaO_2 (%)	97.00 (96.00–98.00)	97.00 (96.00–97.00)	98.00 (97.00–98.00)	<0.0001
Minimum SaO_2 (%)	89.00(85.00–92.00)	86.00(81.00–89.00)	92.00(90.00–94.00)	<0.0001
Sleep efficiency (%)	93.30 (85.60–96.20)	93.20 (86.78–96.13)	93.80 (85.50–96.30)	0.813
Respiratory arousal index	0.60 (0.00–2.10)	1.75 (1.00–3.98)	0.00 (0.00–0.10)	<0.0001
REM respiratory arousal index	0.60 (0.00–3.30)	2.60 (0.73–5.20)	0.00 (0.00–0.00)	<0.0001
NREM respiratory arousal index	0.50 (0.00–1.90)	1.35 (0.63–3.48)	0.00 (0.00–0.10)	<0.0001

PSG, polysomnography; AHI, apnea-hypopnea index; OAI, obstructive apnea index; OAHI, obstructive apnea-hypopnea index; REM–RDI, rapid eye movement–respiratory disturbance index; NREM–RDI, non–rapid eye movement–respiratory disturbance index; SaO_2, arterial oxygen saturation; OSA, obstructive sleep apnea; PS, primary snoring. Nonparametric test has been applied to investigate for between group differences.

TABLE 3 Comparisons of cognitive and behavioral function tests between groups.

	All	OSA patients	PS patients	Control	*P*
Conduct problem[a]	0.45 (0.07–0.65)	0.38 (0.00–0.90)	0.45 (0.17–0.55)	0.42 (0.17–0.58)	0.773
Learning problem[a]	1.00 (0.50–1.25)	1.00 (0.53–1.25)	0.85 (0.50–1.25)	0.75 (0.25–1.00)	<0.05
Somatic complaints[a]	0.20 (0.00–0.40)	0.20 (0.00–0.40)	0.00 (0.00–0.20)	0.00 (0.00–0.40)	0.077
Hyperactivity[a]	0.75 (0.50–1.25)	0.75 (0.50–1.25)	0.75 (0.50–1.25)	0.50 (0.25–1.00)	<0.05
CIH[a]	0.40 (0.20–0.80)	0.45 (0.33–0.80)	0.40 (0.20–0.90)	0.50 (0.20–0.95)	0.786
Anxiety[a]	0.30 (0.00–0.50)	0.40 (0.25–0.50)	0.25 (0.00–0.75)	0.25 (0.00–0.50)	0.921
PIQ[b]	94.70 ± 13.76	91.07 ± 12.27	99.26 ± 14.34	N/A	<0.01
VIQ[b]	96.78 ± 13.48	93.55 ± 12,42	100.86 ± 13.82	N/A	<0.05
FIQ[b]	93.47 ± 14.56	89.91 ± 12.38	97.94 ± 15.99	N/A	<0.05

CIH, Conners' index of hyperactivity; PIQ, Performance intelligence quotient; VIQ, Verbal intelligence quotient; FIQ, Full intelligence quotient; OSA, Obstructive sleep apnea; PS, Primary snoring.
[a]Nonparametric test.
[b]The student's *t* test.

TABLE 4 Comparisons of BDNF, trkB, IL-1β and TNF-α among three groups.

Variables	OSA patients	PS patients	Control	*P*
BDNF (ng/ml)	1.22 ± 0.63	1.78 ± 1.01	2.35 ± 1.30	<0.001
TrkB (ng/ml)	1.21 ± 0.55	1.62 ± 0.99	2.24 ± 1.07	<0.001
TNF-α (pg/ml)	284.59 ± 122.76	194.88 ± 121.21	13.89 ± 8.74	<0.001
IL-1β (pg/ml)	6.80 ± 5.65	4.61 ± 3.86	1.45 ± 0.26	<0.001

BDNF, Brain–derived neurotrophic factor; TrkB, Tyrosine kinase receptor B; IL–1β, interleukin–1beta; TNF–α, tumor necrosis factor–alpha; OSA, obstructive sleep apnea; PS, primary snoring. Analysis of variance test has been applied to investigate for between group differences.

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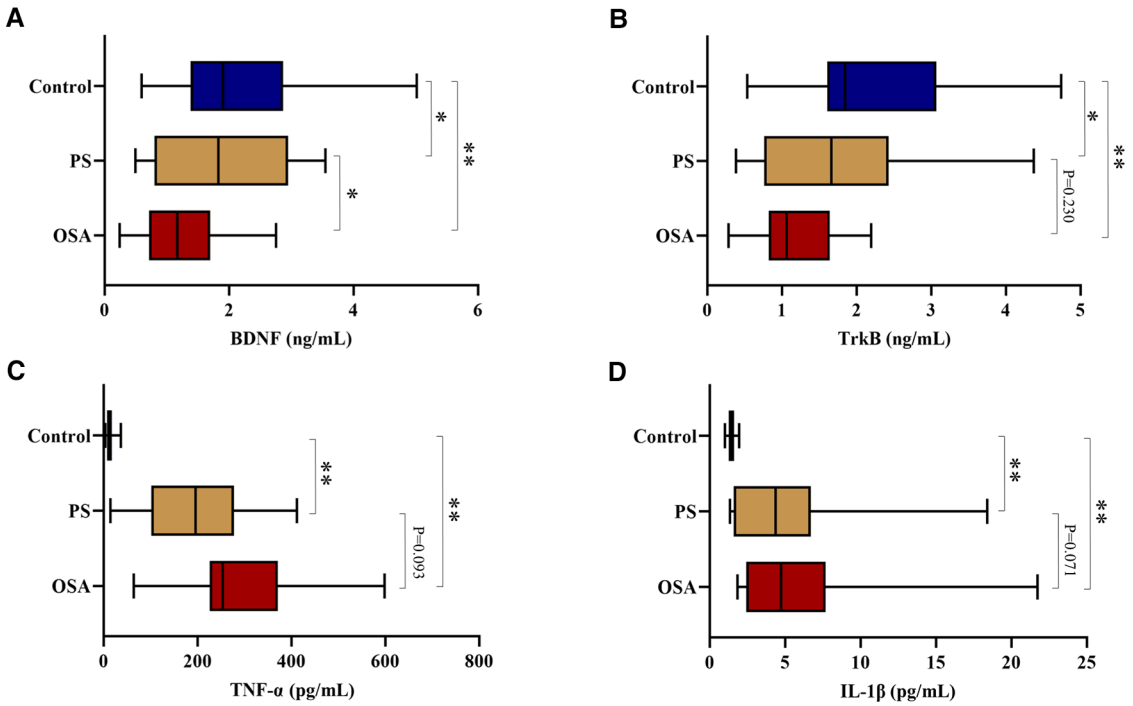

FIGURE 2
(A) Comparison of serum BDNF levels among three groups; (B) Comparison of serum TrkB levels among three groups; (C) Comparison of serum TNF-α levels among three groups; (D) Comparison of serum IL-1β levels among three groups. $^{**}P < 0.01$, $^{*}P < 0.05$. BDNF, brain-derived neurotrophic factor; TrkB, tyrosine kinase receptor B; IL-1β, interleukin-1beta; TNF-α, tumor necrosis factor-alpha.

Discussion

In this study, we investigated the relationship between cognitive status and serum BDNF and TrkB in OSA and PS children. In addition, we discovered that the serum BDNF level in children with SDB was lower than that of the control group, especially in the OSA group. Furthermore, we revealed a correlation between OSA status, TrkB, and course of mouth breathing and cognitive status through logistic regression analysis.

In the present study, we found that the maternal education level in the OSA group was significantly lower compared to the control group. This may suggest that mothers with high educational levels were more conducive to their children's early medical treatment. Interestingly, no significant difference was found between BMI and BMI-Z scores between the groups, which was not consistent with a previous study (2). This may be caused by the outdated belief that heavier children were closely associated with snoring, thus resulting in a higher diagnosis among heavier children. However, this still needs to be verified by larger sample sizes in the future.

Over the past several decades, numerous studies have shown that children who suffer from SDB are at great risk for behavioral disorders, which may manifest in a variety of ways. The most commonly observed disorders are hyperactivity disorder, attention disorder, and somatic complaints (17, 24). According to the results of CPRS among the three groups, the OSA children were found to have behavioral disorders, mainly learning problems and hyperactivity, whereas the PS children did not show any obvious behavioral disorders when compared with the control group. We observed that the average scores of the PS children were much higher than those of the control group. We speculated that this might be because PS children generally have a shorter course of the disease and inconspicuous symptoms than OSA children. Thus, PS children received less attention from parents, which in turn affected parents' subjective tendencies when filling out the scale. Consequently, further validation by large sample studies is required.

We used C-WISC combined with BNDF and TrkB to explore the cognitive impairment in children with SDB. The comparison of intelligence between the two groups showed that VIQ, PIQ, and FIQ of OSA children were significantly lower than those of PS children, indicating that the cognitive functions were worse in children from the OSA group. Regrettably, we were unable to assess the level of cognitive impairment in PS children because of the lack of C-WISC scores for children in the control group. Nevertheless, compared with the C-WISC scores of normal children in previous studies (25), the scores of PIQ, VIQ, and FIQ in the PS group were not significantly lower. However, this did not suggest that cognitive impairment does not exist in PS

TABLE 5 Correlation analysis between baseline characteristics, inflammatory indicators, behavioral and cognitive parameters.

Variables	BNDF		TrkB		TNF-α		IL-1β	
	Correlation coefficient	*P*	correlation coefficient	*P*	correlation coefficient	*P*	correlation coefficient	*P*
BDNF	1.000	-	0.919	<0.01	−0.507	<0.001	−0.312	<0.01
TrkB	0.919	<0.01	1.000	-	−0.570	<0.001	−0.350	<0.01
TNF-α	−0.507	<0.01	−0.570	<0.01	1.000	-	0.741	<0.01
IL-1β	−0.312	<0.01	−0.350	<0.01	0.741	<0.001	1.000	-
Course of snoring	−0.147	0.110	−0.214	<0.05	0.588	<0.001	0.498	<0.01
Course of mouth breathing	−0.194	<0.05	−0.240	<0.01	0.590	<0.001	0.575	<0.01
Course of choking	−0.170	0.065	−0.232	<0.05	0.446	<0.001	0.419	<0.01
Epworth sleepiness scale	−0.065	0.483	−0.067	0.467	0.050	0.593	0.120	0.192
BMI	−0.073	0.429	−0.071	0.441	−0.017	0.857	−0.340	0.711
BMI-Z score	−0.033	0.718	−0.50	0.592	−0.034	0.711	−0.095	0.302
A/N ratio	−0.204	0.071	−0.186	0.101	−0.038	0.740	−0.007	0.948
Tonsil size	−0.242	<0.05	−0.199	0.079	0.075	0.511	0.014	0.905
Maternal education level	0.135	0.143	0.079	0.393	−0.055	0.553	−0.153	0.097
OAHI	−0.315	<0.01	−0.224	<0.05	0.261	<0.05	0.264	<0.05
REM-RDI	−0.195	0.084	−0.129	0.257	0.278	<0.05	0.246	<0.05
NREM-RDI	−0.356	<0.01	−0.261	<0.05	0.323	<0.01	0.302	<0.01
Conduct problem	−0.090	0.330	−0.062	0.505	−0.009	0.920	−0.044	0.636
Learning problem	0.002	0.984	0.052	0.575	0.199	<0.05	0.184	<0.05
Somatic complaints	−0.091	0.327	−0.074	0.424	0.180	0.050	0.233	<0.05
hyperactivity	−0.241	<0.01	−0.206	<0.05	0.272	<0.01	0.210	<0.05
Anxiety	0.187	<0.05	0.151	0.101	−0.082	0.377	0.058	0.532
CIH	−0.029	0.754	0.008	0.119	−0.051	0.585	−0.012	0.895
FIQ	0.249	<0.05	0.316	<0.01	−0.218	0.054	−0.117	0.304
VIQ	0.317	<0.01	0.220	0.051	−0.246	<0.05	−0.135	0.237
PIQ	0.300	<0.01	0.307	<0.01	−0.272	<0.05	−0.146	0.199

BDNF, brain–derived neurotrophic factor; TrkB, tyrosine kinase receptor B; IL-1β, interleukin-1beta; TNF-α, tumor necrosis factor-alpha; BMI, body mass index; OAHI, obstructive apnea-hypopnea index; REM-RDI, rapid eye movement-respiratory disturbance index; NREM-RDI, non-rapid eye movement-respiratory disturbance index; CIH, Conners' index of hyperactivity; FIQ, full intelligence quotient; VIQ, verbal intelligence quotient; PIQ, performance intelligence quotient.

children. As our results revealed a significant increase in inflammatory factors and a decrease in BDNF and TrkB in PS children like OSA children, this suggested that PS children experienced similar inflammatory responses and nerve injury as OSA children. Nonetheless, we did not find weak hypoxia or arousal in PS children, which may be caused by the lack of precision and interpretation accuracy of PSG. It is also possible that hypoxia or arousal in PS children did not happen during PSG detection. It is necessary to acknowledge that even though PSG suggests that PS children do not have nocturnal hypoxia, this does not mean that they do not have cerebral-level hypoxia.

A few studies have looked at the relationship between BDNF and OSA in adults and showed conflicting results, as some have found a relationship between BDNF and OSA (26, 27), whereas others reported no significant difference (28, 29). In addition, the association between circulating levels of BDNF and children with SDB is also still unclear. Consistent with our findings, Bahgat et al. have previously shown that OSA children have lower serum BDNF levels than healthy controls

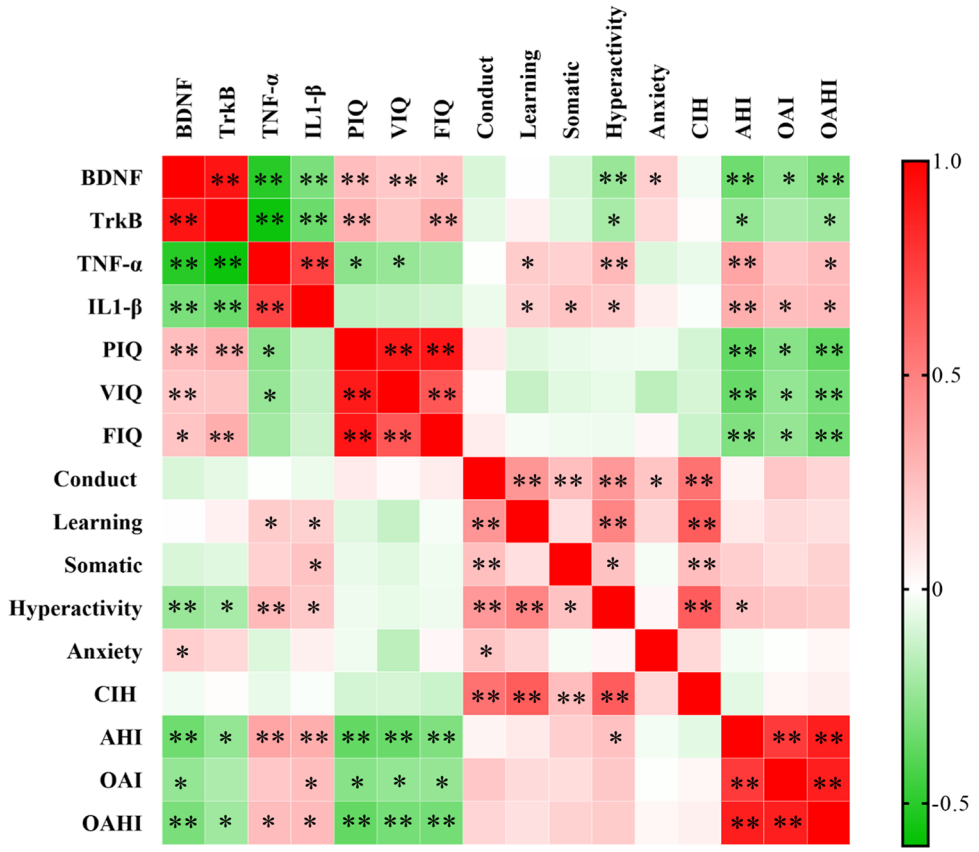

FIGURE 3
Correlation analysis between BDNF, TrkB, IL-1β, TNF-α, and cognitive parameters. $^{**}P < 0.01$, $^{*}P < 0.05$. BDNF, brain-derived neurotrophic factor; TrkB, tyrosine kinase receptor B; IL-1β, interleukin-1beta; TNF-α, tumor necrosis factor-alpha.

TABLE 6 Results of the logistic regression analysis: assessing the risk of abnormal intelligence in relation to different independent variables.

Variables	Unadjusted odds ratio (95% CI)	*P*	Adjusted odds ratio (95% CI)	*P*
OSA status				
OSA	4.802 (1.678–13.744)	<0.01	4.582 (1.496–14.034)	<0.01
Non-OSA	Ref	Ref	Ref	Ref
Couse of mouse breathing	1.045 (1.014–1.077)	<0.01	1.043 (1.010–1.077)	0.01
TrkB	0.373 (0.166–0.839)	<0.05	0.362 (0.157–0.836)	<0.05

TrkB, tyrosine kinase receptor B; OSA, obstructive sleep apnea; CI, confidence interval; Adjusted models controlled for age, sex and BMI-Z score.

(30). Moreover, a significant difference was also found in serum BDNF levels between OSA children and PS children. In contrast, studies by Makhout et al. and Wang et al. have shown that BDNF levels are not affected by OSA in children (31, 32). The results and patients were not evaluated in terms of OAHI ≥ 1 in these studies, which could explain the discrepancy in the results. However, these studies failed to explore the relationship between BDNF and PS children and the relationship between BDNF and cognition. At the same time, correlation analysis showed a good correlation between the level of serum BNDF and the cognitive scores in our study, indicating that the higher the level of serum BDNF, the better the score of cognitive assessment, and suggesting that BDNF may reflect the severity of cognitive impairment in children with SDB. Interestingly, children with lower serum TrkB levels, but not serum BDNF, were at a higher risk of abnormal intelligence. This suggests that TrkB, a receptor for multiple neurotrophins (BDNF and neurotrophin 4) (33), may

be a more sensitive and worthy indicator of cognitive impairment than serum BDNF. In addition, serum TrkB is a marker that is easier to detect than BDNF, which is unstable in blood (34).

As a harmful consequence induced by chronic IH, apoptotic neuronal cell death is strongly believed to contribute to cognitive impairment in OSA disease, as shown in animal models and clinical studies (35, 36). And may be a major medium. As previously mentioned, chronic IH associated with SDB can lead to the release of pro-inflammatory cytokines that activate apoptotic signals and damage the hippocampus and neurons (10), which may contribute to the decline in BDNF and TrkB expression. The decline of BDNF and TrkB further aggravates neurological damage and eventually leads to cognitive impairment (7). The present study also confirmed the aforementioned results, as we found that the inflammatory factors TNF-α and IL-1β were significantly increased in children with SDB and that TNF-α was negatively correlated with VIQ and PIQ, thus suggesting that the inflammatory response in children with SDB may affect their cognitive status. Moreover, both BDNF and TrkB were negatively correlated with TNF-α and IL-1β, which may indicate that the inflammatory response has a certain inhibitory effect on the expression of BDNF and TrkB. This also explained why there were significant differences in BDNF rather than IL-1β and TNF-α between PS and OSA groups, as inflammatory markers appeared relatively earlier.

To the best of our knowledge, the current study is the first to assess the relationship between cognitive status and serum BDNF, TrkB in children with OSA and PS. Nonetheless, present study still has some limitations. First, future large-scale, multicenter, hospital-community prospective studies are needed to assess whether BDNF can reflect the degree of cognitive impairment and whether it can be used as a reliable predictor of cognitive impairment in children with SDB. Second, in our study, we included only younger children (3–12 years), therefore, our results cannot be interpolated to older children and adolescents. Third, in the control group, we excluded children with SDB by using the medical history, Pediatric Sleep Questionnaire, and physical examination, and we did not perform PSG and C-WISC.

Conclusion

Our findings showed that serum BDNF and TrkB in OSA and PS children were lower than those in the control group and that serum BDNF was positively correlated with PIQ, FIQ, and VIQ. Serum BDNF and TrkB levels may be promising biological indicators reflecting the severity of cognitive impairment and predicting cognitive impairment in children with SDB.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Second Affiliated Hospital of Xi'an Jiaotong University (approval no. 2017058). The patients/participants provided their written informed consent to participate in this study.

Author contributions

YS, and XR designed the research. YF, and LM wrote the manuscript. YF, XC, and LM performed the experiments. ZC, YZ, and HL participated in the collection of data. YY, LM, and YX performed the statistical analysis. XR directed the research. All authors reviewed the results and approved the final version of the manuscript. XR is the guarantor of the paper who takes full responsibility for the integrity of the work, from its inception to the published article. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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.

Publisher's note

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Reduced circulating growth hormone and insulin-like growth factor-1 and delayed growth of premature rats are aggravated by longer daily duration of chronic intermittent hypoxia exposure

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Objective: This study mainly aimed to investigate the effect of daily duration of chronic intermittent hypoxia (CIH) exposure on circulating growth hormone (GH)/insulin-like growth factor-1 (IGF-1) concentrations and body weight changes of premature rats.
Methods: 40 healthy male SD rats aged six weeks were enrolled in this study. These rats were randomly divided into four groups ($n = 10$ per group), including normal control (NC) group (normal oxygen exposure every day), CIH-1 group (daily CIH exposure for 2 h), CIH-2 group (daily CIH exposure for 4 h), and CIH-3 group (daily CIH exposure for 8 h). The serum GH/IGF-1 concentrations and body weights in all rats were determined after 30 days of normal oxygen or CIH exposure.
Results: No significant difference was found with respect to the baseline body weight among the four groups of rats. After establishments of animal models with a duration of 30 days, significant differences were found respect to body weight, body weight changes, and serum GH/IGF-1 concentrations among the four groups of rats with a same trend (all $P < 0.05$): the highest values were all in NC group rats, followed CIH-1 group, CIH-2 group, and CIH-3 group rats. Among all the rats, the body weight changes correlated significantly with both serum GH and IGF-1 concentrations (both $P < 0.05$).
Conclusion: CIH decreases circulating GH/IGF-1 concentrations and causes growth delay in premature rats. Such effects could be aggravated by increased daily duration of CIH exposures.

KEYWORDS

insulin-like growth factor-1, chronic intermittent hypoxia, growth delay, rat, growth hormone

Introduction

Obstructive sleep apnea (OSA) is characterized by recurrent episodes of partial or complete collapse of upper airway during sleep. The physiological consequences of this disease include sleep fragmentation, intermittent hypoxia, increased sympathetic activation, and nocturnal arousal (1). In children, the prevalence of OSA could reach to 3%–10% (2), and this disease is associated with several comorbidities, including decreased quality of life, worsened mental health, increased cardiovascular problems, and poor growth and development (3–6).

Growth hormone (GH) is a peptide hormone synthesized and secreted by the pituitary gland and its primary function is to promote somatic growth mostly through inducing synthesis of insulin-like growth factor-1 (IGF-1) (7), which are vital for skeletal growth in children (8). Reduced circulating GH/IGF-1 concentrations had been reported to be associated with growth delay in children with OSA (9, 10). In addition to sleep fragmentation, OSA related intermittent hypoxemia is also believed to be an important contributor (11, 12). However, the effect of different daily durations of hypoxemia on serum GH/IGF-1 concentrations is unknown. This is important for therapeutic indication, as hypoxemia always present during part of the whole night sleep in the vast majority of children with OSA.

In current study, immature Sprague Dawley (SD) rats were randomly grouped and subjected to different daily durations of chronic intermittent hypoxia (CIH) environment to simulate OSA associated hypoxemia. The serum GH and IGF-1 concentrations, and the body weight changes were determined and compared between different groups of rats. In particular, it was expected to investigate the effect of different daily duration of CIH exposure on serum GH and IGF-1 concentrations and delay growth of premature rats.

Materials and methods

Experimental animals

40 healthy male SD rats aged six weeks (obtained from Beijing Vital River Laboratory Animal Technology Co., Ltd.) were used in this study. All the rats were allowed free access to food and water, and raised under the conditions of 12 h light/dark cycle, 22 ± 2°C and 40% humidity. The protocol was approved by the Animal Ethics Committee of Peking University First Hospital. The experiments were performed in accordance with the relevant provisions of Regulations of the People's Republic of China on the Administration of Laboratory Animals.

Establishments of CIH models of rats

The exposures of CIH in this study were achieved in a hypoxia chamber, which could be adjusted. 40 SD rats were randomly divided into 4 groups ($n = 10$ per group), including one normal control (NC) group (normal oxygen exposure every day) and three CIH groups. The exposure conditions of the three CIH groups were as follows:

(1) CIH-1 group: The rats were persistently exposed to cycles of 10%–21% O_2 (10% O_2 for 1 min and 21% O_2 for 1 min) in the controlled hypoxia chamber for 2 h per day, 30 days in total;
(2) CIH-2 group: The exposure of CIH and the total duration were both the same with CIH-1 group except the daily exposure duration which was increased to 4 h;
(3) CIH-3 group: The exposure of CIH and the total duration were both the same with CIH-1 and CIH-2 groups except the daily exposure duration which was increased to 8 h.

Body weight measurement and detection of circulating Gh and IGF-1 concentrations

At day 0 and day 30, the weights of all rats were measured and recorded, respectively. At day 30, all the rats were intraperitoneally anesthetized with 4 ml/kg 10% chloral hydrate (0.4 g/kg), and arterial blood samples were harvested from the right femoral artery, respectively. Serum was separated by centrifugation (Eppendorf, Germany) at 3,000 rpm for 15 min and stored at −80°C until analyzed. The circulating GH and IGF-1 concentrations were evaluated by commercially-available ELISA kits (Boster, China), according to the manufacturer's instructions, respectively. The optical density of each well was determined at 450 nm within 30 min.

Statistical analysis

SPSS 20.0 statistical software (SPSS, Inc., Chicago, IL, United States) was used for data processing. Continuous variables were presented as mean ± standard deviation. Comparisons between the groups were evaluated by One-way ANOVA test. Correlation analysis between different variables were evaluated by Pearson correlation test. $P < 0.05$ indicated a significant difference.

Results

After establishments of animal models with a duration of 30 days, only one rat in NC group died before blood sample collection. Therefore, the data of the remaining 39 rats were

collected for further analysis, including 9 cases in NC group and 10 cases in each CIH group.

The body weights measured at day 0 and day 30, the body weight changes, and the serum GH and IGF-1 concentrations detected at day 30 were shown in **Table 1**: No significant difference was found in baseline body weight among the four groups of rats ($P = 0.987$). However, there were significant differences respect to body weight measured at day 30, body weight changes, and serum GH and IGF-1 concentrations detected at day 30 (all $P < 0.05$). Furthermore, the trend was same: the highest values were all in NC group rats, followed CIH-1 group, CIH-2 group, and CIH-3 group rats (as shown in **Figure 1**).

Among all the 39 rats, further analyses showed that the body weight changes correlated significantly with both serum GH ($P = 0.001$) and IGF-1 concentrations ($P = 0.018$) (as shown in **Figure 2**), with correlation coefficients of 0.495 and 0.377, respectively.

Discussion

GH/IGF-1 axis plays essential roles in regulating multiple physiological processes in humans and other species, including in promoting somatic growth in children (13–17). The present study showed that daily CIH exposure could surely reduce circulating GH/IGF-1 concentrations and cause growth retardation *in vivo,* which supported the findings of former clinical studies (18–21). On the other hand, the significant correlations between circulating GH/IGF-1 concentrations and the body weight changes of the rats confirmed the decisive role of this axis in affecting somatic growth caused by CIH. Therefore, the circulating GH/IGF-1 concentrations could be used as reliable indicators to evaluate the effect of OSA on children's growth and development.

In normal children, the maximal GH secretory usually burst during the period of SWS (17, 22). Thus, individuals with OSA, who demonstrate polysomnographic reduction of SWS, may theoretically display alterations in GH/IGF-1 secretions (22). The current results suggested that circulating GH/IGF-1 concentrations could be directly affected by intermittent hypoxemia, another typical pathophysiological change of OSA. Such effect existed even in a short daily duration of CIH exposure, and became more pronounced with prolonged daily durations of CIH exposures. The pathophysiological basis for this time dependency is unknown. However, the clinical implicating is that, even a short duration of sleep hypoxemia per day (two hours in this study) could be proper indication for intervention respect to maintain a normal growth and development.

In clinical work, an in-laboratory polysomnography is not always prescribed for children patients with potential OSA due to its poor compliance, and a nocturnal pulse oximetry has been commonly used as an alternative test. The current results suggested that the latter may also be valuable for evaluating treatment indication, as it could detect the existence of hypoxemia and its duration.

Besides OSA, there were several factors that may affect GH/IGF-1 levels, such as age, genetics, psychological factors, exercise, obesity, nutritional intake, smoking and alcohol status, and even sleep duration (8, 14, 17, 23–27). Therefore, it is hard to exactly explore the effect of OSA related hypoxemia on these two hormone levels in clinical studies. In the present study, rats which had the same species, gender, age, body weights, and diet without smoking and alcohol were enrolled in the study, and the potential bias induced by other factors was excluded to the greatest extent, indicating that our findings above are convincing.

There are some limitations that need to be addressed. First, the number of rats used was relatively small. However, the potential confounders could be well controlled. Second, besides body weight, there were also some other items that could represent growing development, such as skeletal development, cognitive competence, etc., which were not discussed in current study. Third, the specific mechanism by which CIH affects circulating GH/IGF-1 concentrations was not explored in current study. The last two points are the focus of our future research.

TABLE 1 The body weight, body weight changes, and serum GH/IGF-1 concentrations among the four group of rats after 30 days.

	NC ($n = 9$)	CIH-1 ($n = 10$)	CIH-2 ($n = 10$)	CIH-3 ($n = 10$)	*P* value
Body Weight at day 0 (g)	315.6 ± 3.8	316.1 ± 11.1	314.9 ± 12.0	316.2 ± 5.7	0.987
Body Weight at Day 30 (g)	520.9 ± 15.3	508.8 ± 10.6	507.0 ± 9.4	492.9 ± 9.6	<0.001
Weights Changes (g)	205.3 ± 16.7	192.7 ± 8.5	192.1 ± 14.5	176.7 ± 13.7	<0.001
Serum GH (ng/ml)	16.7 ± 2.4	15.8 ± 2.7	15.4 ± 2.4	11.6 ± 2.6	<0.001
Serum IGF-1 (pg/ml)	599.0 ± 241.3	473.1 ± 300.3	328.6 ± 115.4	304.3 ± 207.5	0.026

Conclusions

In summary, our study demonstrated that CIH exposure could decrease circulating GH/IGF-1 concentrations and cause delayed growth in premature rats. The decrease of these two hormones and the delayed growth were in same trends.

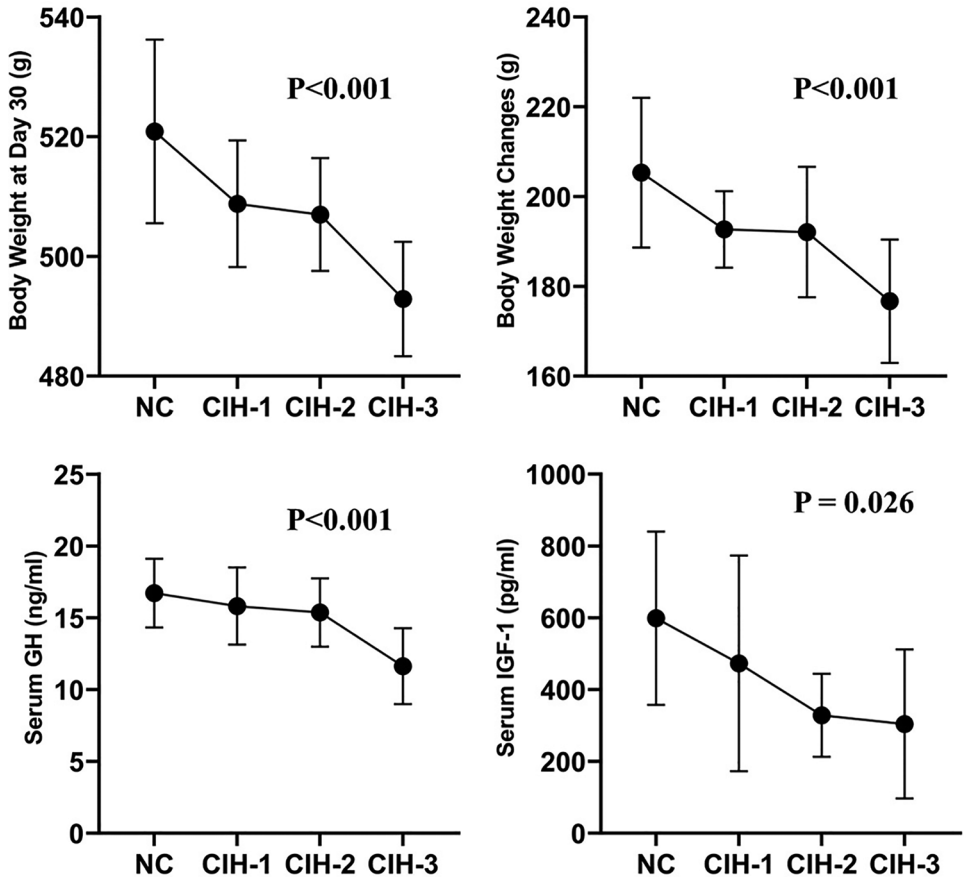

FIGURE 1
Body weight measured at day 30, body weight changes, and serum GH and IGF-1 concentrations detected at day 30 all differed significantly among the four group of rats in a same trend (all $P < 0.05$): the highest values were all in NC group rats, followed CIH-1 group, CIH-2 group, and CIH-3 group rats.

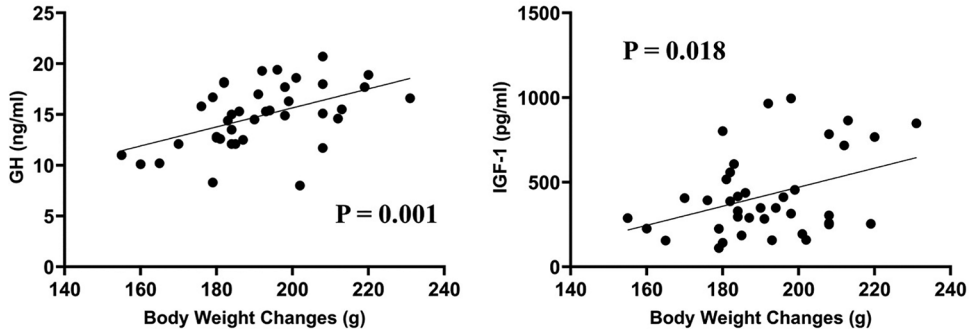

FIGURE 2
Among all the 39 rats, the body weight changes correlated significantly with both serum GH (correlation coefficient = 0.495, $P = 0.001$) and IGF-1 concentrations (correlation coefficient = 0.377, $P = 0.018$).

Moreover, longer daily durations of CIH exposures aggravated the above effects.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The animal study was reviewed and approved by The Animal Ethics Committee of Peking University First Hospital.

Author contributions

JZ and GY: designed the study. CZ, XD and JL: participated in the material preparation and data collection. CZ, XD, JL and JZ: engaged in data analysis and drafting of the manuscript. GY: revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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.

Publisher's note

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Effect of tonsillectomy in a child with obesity and obstructive sleep apnea: A case report and review of the literature

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Obstructive sleep apnea (OSA) is an increasingly recognized disorder in children. Adenotonsillectomy is the primary surgical treatment for OSA in children with adenotonsillar hypertrophy (ATH). We present the case of an obese 4-year-old boy hospitalized for severe desaturation during sleep and severe ATH. Nasal steroid therapy proved ineffective with persistent symptoms. Polygraphy documented severe OSA with an apnea–hypopnea index (AHI) equal to 11. Tonsillectomy resulted in prompt symptom improvement and a substantial reduction of the AHI (2.2). In this case, tonsillectomy alone resulted effective in treating OSA, despite obesity. We concluded that the presence of obesity should not postpone/exclude surgical treatment of preschool children for whom ATH is the most important cause of OSA.

KEYWORDS

OSA (obstructive sleep apnea), obesity, sleep disturbance, sleep-disordered breathing (obstructive/central sleep apnea), adenotonsilar hypertrophy, tonsillectomy

Introduction

Definition

Sleep-disordered breathing (SDB) refers to a wide spectrum of conditions ranging from primary snoring and upper airway resistance syndrome to obstructive sleep apnea (OSA). Primary snoring is defined as snoring without medical comorbidity (1). Upper airway resistance syndrome is characterized by sleep fragmentation with short (1–3 s) arousals preceded by 3–20 s periods of increasing intrathoracic pressure not associated with oxygen desaturation, apnea, or hypopnea (2). OSA is defined by the *American Thoracic Society* as a disorder of breathing during sleep characterized by prolonged partial upper airway obstruction (hypopnea) or intermittent complete obstruction (obstructive apnea) that disrupts normal ventilation during sleep and normal sleep patterns (3).

Epidemiology

OSA occurs at any age, mostly between 2 and 6 years of age, and affects 2%–4% of children (4, 5). In children, OSA has a lower prevalence and no gender difference compared to adults,

Abbreviations
OSA, obstructive sleep apnea; AHI, apnea–hypopnea index; ENT, ear, nose, and throat; AT, adenotonsillectomy; PG, polygraphy; RERA, arousals related to respiratory effort; SDB, sleep-disordered breathing; ATH, adenotonsillar hypertrophy; PSG, polysomnography; CO_2, carbon dioxide; RDI, respiratory disturbance index; DISE, drug-induced sleep endoscopy; MRI, magnetic resonance imaging; CPAP, continuous positive airway pressure.

ranging from 1.1% in preschool age to 4% in school age (6). Two age peaks in the incidence of OSA in children were described: the first one between 2 and 8 years of age, mostly due to adenotonsillar hypertrophy (ATH), and the second one during adolescence related to weight gain (6).

Based on the underlying pathophysiological mechanism, three clinical phenotypes of pediatric OSA are defined: type I associated with ATH, type II associated mainly with obesity, and type III associated with craniofacial dysmorphism of congenital syndromes (Crouzon syndrome, Arnold–Chiari malformation, Pierre-Robin syndrome, Down syndrome, achondroplasia, etc.) (6). ATH and obesity are the major risk factors for OSA in otherwise healthy children (7). The prevalence of OSA in obese children rises to 60% (8). Conditions that reduce upper airway size (such as craniofacial anomalies) or that affect neural control (such as cerebral palsy) or upper airway collapsibility (such as muscular dystrophy or other neuromuscular disorders) are other risk factors for OSA (9).

Several studies suggested that allergic rhinitis is a risk factor for SDB in children with ATH (10, 11). A systematic review demonstrated a higher prevalence of SDB in children with allergic rhinitis (10). ATH in children with allergic rhinitis could be due to the immunologic response to antigens and other inflammatory stimuli (11). To date, allergic or nonallergic rhinitis is considered a symptom enhancer rather than risk factor for OSA (12).

An increased risk of SDB in childhood was also identified in premature infants, in children with a family history of OSA, and in the African-American ethnicity (13).

Clinical manifestations

Clinical manifestations of OSA are both nocturnal and daytime symptoms. Although snoring is present in nearly all children with OSA, it is characterized by a low specificity for OSA and cannot reliably distinguish OSA from primary snoring (5). Other nocturnal symptoms include mouth breathing, noisy breathing, pauses in breathing, coughing, or choking in sleep, restless sleep, and nighttime sweating. Nocturnal enuresis and parasomnias such as sleepwalking and sleep terrors are common but less well-recognized symptoms (14).

Daytime sleepiness may manifest as age-inappropriate daytime napping, complaints of sleepiness, or falling asleep during school, short car rides, or on the school bus (15). Mouth breathing or hyponasal speech is common in children with OSA due to its association with adenoidal hypertrophy (16).

Chronic exposure to intermittent hypoxemia and sleep deprivation could lead to neurobehavioral sequelae (5). Behavioral (hyperactivity, impulsivity, rebelliousness, and aggression) and neurocognitive (inattention and learning problems) problems sometimes lead to a misdiagnosis of attention deficit hyperactivity disorder (14).

Severe OSA can be associated with failure to thrive, probably due to the increased energy expenditure for the elevated work of breathing during sleep (17) and the reduced production of growth hormone during disturbed sleep (6).

Furthermore, several studies demonstrated that OSA in children is associated with metabolic, cardiovascular, and neurocognitive complications (15, 18–21). In a 20-year follow-up study of adults with polysomnography (PSG)-documented OSA between 1 and 17 years of age, subjects with severe OSA showed significantly higher BMI, lower academic qualifications, and higher incidence of snoring than a healthy control group. Furthermore, apnea–hypopnea index (AHI) tended to predict cardiovascular outcomes during childhood (21).

At last, symptoms of OSA in children depend on the developmental stage. Disturbed sleep with frequent changes of position and nightmares, growth defects, and behavioral disorders such as hyperactivity and inattention are mostly described in preschool age. Excessive sweating, pavor nocturnus and somnambulism during sleep, hyporexia, learning disabilities, daytime sleepiness, emotional instability, difficulty in morning awakening, bruxism, and diurnal headaches are more common in school age (6).

Diagnosis

Early diagnosis and treatment of OSA could decrease morbidity. However, diagnosis is frequently delayed (22).

OSA is mostly suspected when specific signs and symptoms were reported by parents or identified by a physical examination (13). History and physical examination are useful for screening subjects who need further investigations but are insufficient to diagnose OSA (6). Measures such as tonsil size assessment, questionnaires, sleep videos, and nocturnal oximetry showed notable variability and inaccuracy in identifying children with OSA (23), and they are mostly used as screening tools in low-resource settings.

PSG is the gold standard for the diagnosis and severity assessment of OSA. PSG is the simultaneous recording of multiple physiological signals during sleep including activity of the brain, heart, eyes, and muscles (24). According to the *American Academy of Otolaryngology—Head and Neck Surgery Foundation*, PSG is indicated in children with SDB and complex medical conditions (obesity, Down syndrome, craniofacial abnormalities, neuromuscular disorders, sickle cell disease, mucopolysaccharidoses) before determining the need for tonsillectomy and in children with SDB and discordance between the tonsillar size and the reported severity of SDB (25, 26).

Sleep and associated events are scored according to the *American Academy of Sleep Medicine Manual* guidelines since 2007 (27), periodically updated (28, 29). Specific guidelines for scoring pediatric sleep were included in the 2007 update (27, 30). During PSG, multiple sensors are used: nasal and oral airflow sensors, snoring microphones, respiratory impedance plethysmographs, pulse oximetry sensors, electrocardiograms, carbon dioxide (CO_2) sensors, electroencephalography instruments, and body position monitoring systems. Measurement of these variables permits detection of events and calculation of summary measures for the diagnosis and severity assessment of OSA (30–32):

- AHI: the number of apneas plus hypopneas per hour of sleep. AHI > 1 is considered suggestive of OSA in children. AHI between 1 and 4 indicates mild OSA syndrome, AHI between 5 and 9 indicates moderate OSA syndrome, and AHI ≥ 10 indicates severe OSA syndrome;

- Respiratory disturbance index (RDI): the number of apneas, hypopneas, and arousals related to respiratory efforts (RERAs) per hour of sleep; RDI represents the severity parameter; and
- Hypoventilation: end-tidal or transcutaneous $CO_2 > 50$ mmHg that persists for more than 25% of the total sleep time.

Given the higher respiratory rate in children compared to adults, the duration of sleep respiratory events was considered differently in defining the pathological respiratory events during sleep (6). While the obstructive event duration in adults must be at least 10 s, the pediatric scoring criteria state that obstructive apneas, hypopneas, and RERA must last ≥2 respiratory cycles (24, 32).

The severity definition differs in children compared to adults: AHI ≥ 5 represents the cutoff for a therapeutic need in children to avoid long-term sequelae; conversely, it is the lower limit value for the definition of disease in adults (6).

At last, awake flexible laryngoscopy, drug-induced sleep endoscopy (DISE), and drug-induced sleep cine magnetic resonance imaging (MRI) are useful diagnostic tools to identify anatomic sites of obstruction in children with OSA. Indeed, findings of endoscopy guide appropriate surgical intervention or identify the level of obstruction in the case of residual OSA after surgical treatment. Similarly, Cine-MRI is a promising tool in children with persistent OSA after AT evaluating the size and volume of the upper airway lumen and surrounding soft tissues (13).

Treatment

OSA syndrome in children is a heterogeneous condition with different treatment options. The treatment strategy depends on child's age, underlying etiology, disease severity, PSG findings, comorbidities, and patient beliefs (31, 33).

Surgical treatment with adenoidectomy, tonsillectomy, or AT is the first-line treatment for children with moderate-to-severe OSA syndrome (AHI ≥ 5) aged >2 years old and enlarged adenoids or tonsils (6, 34). It is a safe procedure, with 93% of patients without perioperative complications and a success rate of 75%. Postoperative PSG typically shows a major decrease in obstructive events (23).

Adenoidectomy or tonsillectomy alone may not be sufficient because residual lymphoid tissue may contribute to persistent obstruction (23).

In addition to the risks related to anesthesia, the most common complications include nausea, vomiting, postoperative pain, and bleeding. Less common complications are dehydration, referred otalgia, postobstructive pulmonary edema, velopharyngeal insufficiency, and nasopharyngeal stenosis (35).

Residual OSA after AT is common. Recently, Alsufyani et al. (36) investigated predictors of AT failure in 382 children with SDB. The authors identified chronic rhinitis, obesity, deviated nasal septum, small tonsil size, and age older than 7 years as independent predictors of treatment failure.

A recent retrospective study of 139 children with OSA investigated the less effectiveness of AT in obese children compared to normal-weight ones and found an association between body mass index and circumferential upper airway collapse during DISE. The authors showed that continuous positive airway pressure (CPAP) is more effective compared to AT in children with circumferential collapse (37).

Adenoidectomy alone could be considered, especially in children younger than 2 years of age, to avoid life-threatening hemorrhage in young patients (38).

CPAP is considered a second-line therapy for residual OSA post-AT or bridging therapy before surgery. It is considered a first-line therapeutic option for children who prefer not to undergo surgery, those with minimally enlarged lymph adenoid tissues not indicated for AT, or those with comorbidities with multilevel obstruction, such as obesity and craniofacial syndromes (33).

Medical options could be the best choice for children with an AHI ≥ 1 but <5. Based on the evidence of inflammation and the coexistence of rhinitis and asthma in OSA, anti-inflammatory medications, mainly intranasal corticosteroids and oral montelukast, were used as adjunctive treatments (6, 39).

At last, dental/orthodontic treatment options have emerged in the past decade for children with OSA and orofacial abnormalities. These include rapid maxillary expansion, mandibular advancement appliance, or maxillo-mandibular surgery (40).

A re-evaluation 6–8 weeks after treatment and instrumental tests in patients with residual symptoms are recommended (41).

Case description

A Caucasian 4-year-old boy was admitted to the Pediatric Department for parent-reported episodes of sleep apnea in the last 3 months. Nocturnal symptoms were snoring, mouth breathing, and excessive sweating; daytime symptoms were asthenia, daytime sleepiness, inattention, and reduced school performance.

The child suffered from recurrent upper airway infections and chronic obstructive rhinitis since the age of 18 months. For this reason, some investigations were performed on the child between 2.5 and 3 years of age. The immunological evaluation by cell blood count and serum immunoglobulin and lymphocyte subpopulation dosage resulted in normal; the allergy evaluation by a skin prick test and the dosage of total and specific immunoglobulin E for the main food and respiratory allergens resulted in normal; the ear, nose, and throat (ENT) evaluation found severe tonsillar hypertrophy and indicated an adenotonsillectomy (AT). While waiting for surgery, the child underwent unsuccessful therapy with nasal steroids.

Additionally, the child began to present a weight gain from 3 years of age. The parents reported that the weight gain began with the increasing use of oral cortisone. At 4 years of age, the child was obese, with a body weight of 25 kg and a height of 116 cm, resulting in a body mass index of 18.6 kg/m^2 (98th percentile).

Polygraphy (PG) was performed 2 weeks before admission. The study was recorded on a *Philips Respironics Alice PDx* device with pediatric sensors.

PG lasted 477 min and documented 24 obstructive apneas, 14 central apneas, 39 hypopneas, 9 mixed apneas, and no RERA. The mean oxygen saturation values resulted in 98%, with a minimum of 72%. The percentage of sleep time spent with oxyhemoglobin saturation of less than 90% was 0.6%. The mean heart rate was 83.7 beats per minute (bpm). The patient frequently changed

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position during monitoring. Flow limitations were detected in all the positions during sleep analysis. Therefore, PG documented severe OSA syndrome with an AHI equal to 11, 3.1 episodes of obstructive apnea, and 1.8 episodes of central apnea in 1 h.

After PG, a second ENT consultation documented "no polyps in the nasal cavities or deviation of the nasal septum; mild adenoid hypertrophy; tonsillar gigantism; no anatomical anomalies of the oral cavity and no post-nasal drip; opaque tympanic membranes" (**Figure 1**) and indicated a prompt surgical removal of the tonsils to facilitate airflow through the airways. A dissection tonsillectomy in the Rose position (open technique) was performed with no following complications.

PG was performed 3 weeks after tonsillectomy; the test lasted 509 min and documented 1 obstructive apnea, 3 central apneas, 12 hypopneas, 3 mixed apneas, and no RERA. The mean oxygen saturation values was 97%, with a minimum of 93%. The mean heart rate was 72.3 bpm. PG showed a substantial reduction of AHI (2.2). The PG report before and after the surgical treatment is shown in **Table 1**.

At the follow-up visit 1 month after the surgical procedure, the parents reported complete disappearance of nocturnal symptoms and an improvement in daytime sleepiness. Four months after surgery, the parents reported a remarkable improvement in the quality of life, thanks to the disappearance of nocturnal symptoms and less daytime sleepiness. Unfortunately, the child was still obese and had recurrent respiratory infections. A further allergy and immunological function evaluation showed only a slight increase in dust mite-specific immunoglobulin E (0.55 kUA/L).

Figure 2 shows the timeline of the clinical course of the child before and after surgery.

Written informed consent was obtained from the minor's legal guardian.

TABLE 1 Polygraphy report before and after the surgical treatment. Polygraphy before surgery lasted 477 min and documented 24 obstructive apneas, 14 central apneas, 39 hypopneas, 9 mixed apneas, and no arousals related to respiratory effort (RERA). The mean oxygen saturation values was 98%, with a minimum of 72%. The percentage of sleep time spent with oxyhemoglobin saturation of less than 90% was 0.6%. Polygraphy (PG) documented severe obstructive sleep apnea syndrome with an apnea–hypopnea index (AHI) equal to 11, 3.1 episodes of obstructive apnea, 1.8 episodes of central apnea in 1 h, and the lowest desaturation value of 72%. Three weeks after surgery, PG lasted 509 min and documented 1 obstructive apnea, 3 central apneas, 12 hypopneas, 3 mixed apneas, and no RERA. The mean oxygen saturation values was 97%, with a minimum of 93%. PG showed a substantial reduction of AHI (2.2).

	Before tonsillectomy	After tonsillectomy
Respiratory events		
Central apnea (*n*)	14	3
Obstructive apnea (*n*)	24	1
Mixed apnea (*n*)	9	3
Hypopnea (*n*)	39	12
Apnea + hypopnea (*n*)	86	19
RERA (*n*)	0	0
Total (*n*)	86	19
Oximetry summary		
Total sleep time $SpO_2 < 90\%$ (min)	2.8	0.0
Mean SpO_2 (%)	98	97
Total desaturations (*n*)	68	22
Oxygen desaturation index (*n*/h)	12.9	2.6
Desaturation max (%)	6	5
Duration max desaturation (s)	56	44
Lowest sleep SpO_2 (%)	72	93
Duration lowest SpO_2 (s)	83	2
Maximum SpO_2 during sleep (%)	100	99
Duration maximum SpO_2 (s)	569	45
Mean heart rate (bpm)	83.7	72.3
Snoring summary		
Snoring episodes (*n*)	5	23
Total duration with snoring (min)	0.6	2.6
Mean snoring duration (s)	6.8	6.8
Percentage of snoring (%)	0.1	0.5
Apnea–hypopnea index (AHI)	11.0	2.2
Obstructive apnea for hour (OAI)	3.1	0.1
Central apnea for hour (CAI)	1.8	0.4

Discussion

Symptoms of OSA in our patient started at 4 years of age, in line with the literature; indeed, OSA in children occurs mostly between 2 and 6 years of age (4, 5). The child's parents complained of snoring, which is the most common symptom of OSA (5). The parents also reported pauses in breathing but no other nocturnal symptoms, although these were common but less recognized (14).

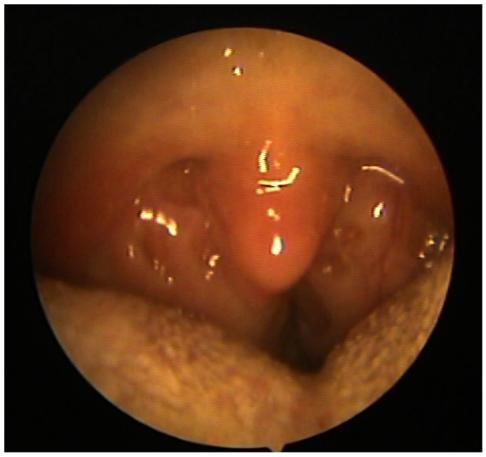

FIGURE 1
Ear, nose, and throat specialist found severe tonsillar hypertrophy (*kissing tonsils*).

The child also suffered from daytime sleepiness, usually more common in school age (6), while daytime symptoms of OSA typical of preschool age (as behavioral disorders) were not reported.

The child also complained of chronic nasal obstruction. Rhinitis often coexists with OSA, and patients with OSA report nasal

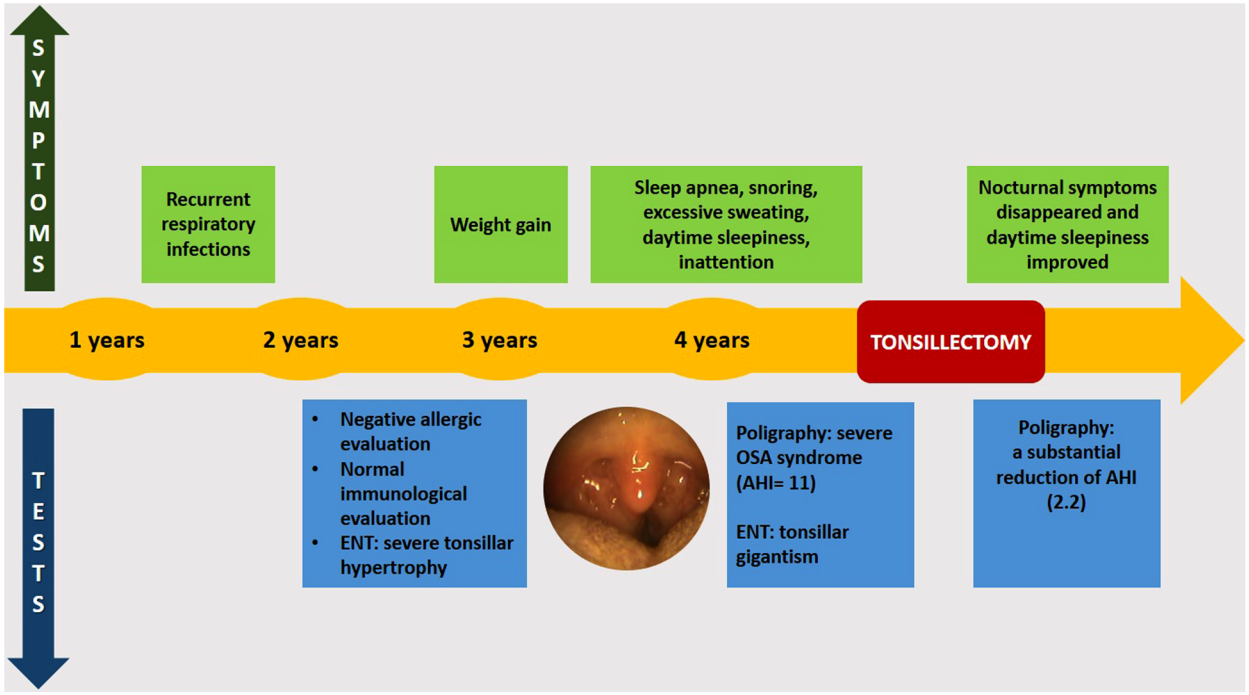

FIGURE 2
Timeline of the clinical course before and after surgery. ENT, ear, nose, and throat; OSA, obstructive sleep apnea; AHI, apnea–hypopnea index.

obstruction in 54% of cases (42, 43). Our patient was not allergic, but a nasal provocation test or nasal cytology to rule out nonallergic rhinitis was not performed. Nevertheless, in our patient, local steroid therapy did not improve symptoms.

In our case, the child presented both major risk factors for OSA: ATH and obesity (7). In children, the type I clinical phenotype of OSA is associated with ATH and occurs mostly between 2 and 8 years of age and the type II phenotype is associated mainly with obesity and occurs mostly in adolescence age (6). Therefore, our patient presented a bridging phenotype between type I and type II.

Although the evidence showed that obesity is a major cause of sleep disorders, it was recently speculated that sleep disorders might cause obesity. In the literature, higher circulating levels of leptin and thus leptin resistance were found in obese patients with OSA compared to obese patients without OSA (44, 45). Hyperleptinemia could originate in response to intermittent hypoxia (46), stimulating food intake in subjects with poor sleep and resulting in a higher risk of developing obesity (45). Conversely, other studies observed no alterations in leptin levels in OSA patients, hypothesizing that increased levels of leptin originated from obesity rather than sleep disorders (47, 48). To date, the causal relationship between obesity and sleep disorders is still unclear. In our patient, it was not possible to establish whether obesity caused OSA or vice versa, as the interval between ATH and obesity and OSA was too short. However, good response to tonsillectomy suggested that ATH was the determinant cause and obesity was an aggravating factor of OSA.

A prompt diagnosis of OSA is important to address an appropriate treatment and avoid complications. In our case, nasal steroid treatment failed, and the clinical evaluation showed tonsillar gigantism and PSG-documented severe OSA syndrome. Therefore, ENT consultation indicated a prompt surgical removal of the tonsils. AT is the first-line treatment for children aged >2 years old with moderate-to-severe OSA and enlarged adenoids or tonsils (6, 33). The child presented chronic rhinitis and obesity, which are predictors of AT failure. Persistent OSA after AT was found in 33%–76% of obese children compared to 15%–37% of nonobese children (49). Therefore, greater efficacy of CPAP compared to AT in obese patients with OSA was suggested (33, 37).

Many studies hypothesized that the patient's age might influence the success rate of AT in obese children (49, 50). The authors suggested that obesity acts as an OSA risk enhancer in younger children, in whom ATH is the main cause of OSA and emerges as a major OSA determinant in older children. In addition, 464 children with OSA were randomly assigned to early AT or a strategy of watchful waiting in a randomized controlled trial. The authors found a significant improvement in symptoms and behavioral, quality-of-life, and polysomnographic findings in the early AT group than in the watchful-waiting group, demonstrating the beneficial effects of early AT (51). The young age of our patient and the presence of ATH were considered more than obesity for the therapeutic choice.

Three weeks after tonsillectomy, PG documented a substantial reduction of AHI (2.2), and a complete regression of symptoms was reported. Surgery success was defined as a postoperative reduction of AHI to <20 and AHI > 50% (52, 53). In our case, the reduction of AHI from 11 to 2.2 showed a positive outcome of the surgery treatment. Tonsillectomy without adenoidectomy produced sufficient results in the child, although a persistent obstruction due to residual lymphoid tissue was reported in the literature (23).

However, a longer follow-up would be needed to identify the long-term effects of surgical therapy.

Conclusion

OSA is a common disorder in children with negative consequences, potentially detrimental to long-term health. An early diagnosis and prompt treatment can prevent cardiovascular, metabolic, and neurocognitive consequences and improve long-term cognitive performance. Therefore, it is necessary to identify, investigate, and promptly treat children with suggestive symptoms and those at risk for OSA syndrome. However, diagnosis and management of OSA syndrome in children are not easy, especially because of the still poor knowledge of the underlying pathogenic mechanisms and the factors influencing the phenotypic variability.

ATH is a predictor of severe OSA, and children with this condition should be prioritized for early PSG and management.

Obesity is another important risk factor for OSA, and the growing number of obese children worldwide is a cause of concern when managing children with OSA. In addition, obesity is a predictor of AT failure. However, the presence of obesity should not postpone/exclude surgical treatment of preschool children for whom ATH is the most important cause of OSA.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material; further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

PDF: wrote the manuscript, led revisions, and created the table and figures; GO: wrote the original draft and created the table; GN: conceived the report and provided the figures and polysomnography data; SDP: supervision; FC: supervision; NR: supervision; MA: supervision and review. All authors have read and agreed to the published version of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

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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Analysis of factors that influence the occurrence of otitis media with effusion in pediatric patients with adenoid hypertrophy

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Objective: Adenoid hypertrophy (AH) and otitis media with effusion (OME) are common pediatric otolaryngological diseases and often occur concurrently. The purpose of this study was to comprehensively analyze the factors that influence the occurrence of OME pediatric patients with AH.

Methods: Patients younger than 12 years with AH, who were hospitalized for treatment at Beijing Tsinghua Changgung Hospital in Beijing, China, between March 2018 and February 2022 were enrolled. The patients were divided into an AH group and an AH + OME group based on the presence of OME. The authors collected the following clinical data for univariable analysis: sex; age; body mass index (BMI); comorbid nasal congestion/rhinorrhea, recurrent tonsillitis, or allergic rhinitis (AR); adenoid and tonsil grade; tonsillar hypertrophy; food/drug allergy; history of adenoidectomy and congenital diseases; breastfeeding status; preterm birth; exposure to environmental tobacco smoke (ETS); family history of adenotonsillectomy, otitis media, and AR; main data of polysomnography and oropharyngeal conditional pathogen culture data of some patients. Univariate analysis was performed as a basis for logistic regression analysis.

Results: A total of 511 children (329 boys and 182 girls) were included, their mean age was 5.37 ± 2.10 years. Of them, 407 (79.6%) were in the AH group and 104 (20.4%) in the AH + OME group. Univariate analysis revealed statistically significant differences in age, BMI, adenoid grade, AR, breastfeeding status, and ETS exposure between the two groups. Multivariate stepwise logistic regression analysis showed that age, adenoid grade, AR, breastfeeding status, and ETS influenced the occurrence of OME in pediatric patients with AH. The risk of OME decreased with increasing age. High adenoid grade, ETS exposure, and comorbid AR were risk factors for OME in pediatric patients with AH, but breastfeeding was a protective factor. The final analytical results of the oropharyngeal conditional pathogen culture data showed that *Streptococcus pneumoniae* positivity was associated with OME in AH.

Conclusion: The pathogenesis of AH with OME is complex. Young age, high adenoid grade, ETS exposure, non-breastfed status, comorbid AR, and the presence of *S. pneumoniae* in the oropharynx are risk factors for OME in pediatric patients with AH.

KEYWORDS

adenoid hypertrophy, otitis media with effusion, influencing factor, obstructive sleep apnea, conditional pathogen

Abbreviations

AH, adenoid hypertrophy; OME, otitis media with effusion; BMI, body mass index; AR, allergic rhinitis; ETS, environmental tobacco smoke; OSA, obstructive sleep apnea; ETD, eustachian tube dysfunction; ET, eustachian tube; PSG, polysomnography; OAI, obstructive apnea index; AHI, apnea hypopnea index; *S. pneumoniae*, *Streptococcus pneumoniae*; *H. influenzae*, *Haemophilus influenzae*; *S. aureus*, *Staphylococcus aureus*; *M. catarrhalis*, *Moraxella catarrhalis*.

1. Introduction

Adenoid hypertrophy (AH) and otitis media with effusion (OME) are common pediatric otolaryngological diseases. Repeated stimulation by bacteria, viruses, and allergens causes pathological AH, resulting in clinical symptoms (1), such as nasal congestion, rhinorrhea, open-mouthed breathing, obstructive sleep apnea (OSA), snoring, and "adenoid face" caused by chronic airway obstruction, which is an important factor that can induce or worsen OME, eustachian tube dysfunction (ETD), and acute/chronic rhinosinusitis in children (2).

OME is a middle ear effusion without an acute middle ear infection. It is most common in children aged six months to four years old. Approximately 90% of preschoolers and 25% of schoolchildren have had OME (3). The prevalence of OME ranges from 1.3% to 31.3% (4) depending on diagnostic methods, race, and environmental factors. However, the pathogenesis and etiology of OME remain unclear. Viral infection, bacterial colonization, allergies, and immune factors can promote the occurrence and progression of OME; mechanical obstruction and ETD also play critical roles. Adenoids obstruct the posterior nostrils and affect ventilation and drainage in the nasal cavity and sinuses, leading to chronic sinusitis. Pathogenic microorganisms and secretions pass through the eustachian tube (ET) and oropharynx to cause ET mucosal inflammation, congestion, edema, and retrograde infection, thereby aggravating or inducing OME (5). AH is the main predisposing factor for OME that often accompanies it in children (6). However, not all pediatric patients with AH develop OME. It is vital to understand the influencing factors associated with OME incidence in pediatric patients with AH. Previous studies have found that atopic or allergic rhinitis (AR), frequent tonsillitis, daycare attendance, exposure to smoke, and multiple family members were major risk factors for OME in pediatric patients with AH (7). Further and more comprehensive analysis of the risk factors for OME in children with AH is needed to provide a reference for the prevention and treatment of such cases and a basis for future in-depth mechanistic studies. Thus, the aim of this study was to comprehensively analyze the factors that influence the occurrence of OME in pediatric patients with AH.

2. Materials and methods

2.1. Study population

In this retrospective study, patients with AH aged ≤12 years old who were hospitalized for treatment at Beijing Tsinghua Changgung Hospital in Beijing, China, between March 2018 and February 2022 were enrolled. The reasons for hospitalization were related clinical symptoms and manifestations of AH, mainly nasal congestion, rhinorrhea, open-mouthed breathing, OSA, snoring, and "adenoid face" caused by chronic airway obstruction. All patients were admitted to the hospital for an adenoidectomy. Some surgeries were combined with tonsillectomy. Two major indications for tonsillectomy and/or adenoidectomy include obstruction and recurrent infection (8). The age limit of 12 years was chosen because the upper age limit in OME guidelines is 12 years (9). Children with OME underwent intraoperative tympanocentesis or tympanostomy tube insertion. During the study period, a total of 518 patients were hospitalized due to the above reasons in an ENT outpatient department at our hospital. Seven were excluded (one case of undetermined neurological disease, one case of nephroblastoma, one case of abnormal coagulation function, one case of hereditary deafness with intellectual disability, one case of middle ear malformation, one case of immune disease, and one case of severe heart disease combined with slow growth). Finally, a total of 511 patients were included as study participants.

The inclusion criteria were as follows: age ≤ 12 years; presence of adenoid tissue obstruction of the posterior nostril (>50%); and presence of nasal congestion, snoring, mouth breathing, and other clinical symptoms. Patients who had acute upper respiratory tract infection in the last 2 weeks that was treated using antibiotics or immune modulators, and patients with cleft palate and other craniofacial deformities; intellectual disability; immunodeficiency; cardiovascular, lung, genetic, autoimmune, and neuromuscular diseases; or other severe underlying diseases were excluded from this study. The included patients were subdivided into an AH group and an AH + OME group based on the presence of OME, and into three groups by age: 0–4 years, 5–8 years, and 9–12 years.

Diagnosis of AH was based on: signs, symptoms, and the results of fiberoptic nasopharyngoscopy, and that of OME was based on: signs, symptoms, and the results of auxiliary examinations (pure tone audiometry/behavioral audiometry, tympanometry, and ear endoscopy), and the intraoperative confirmation of tympanic effusion.

The clinical data of the pediatric patients, including sex; age; body mass index (BMI); comorbid nasal congestion/rhinorrhea (mucoid or mucopurulent), recurrent tonsillitis, or AR; adenoid grade; tonsil grade; tonsillar hypertrophy; food/drug allergy; history of adenoidectomy; history of congenital diseases; breastfeeding status; preterm birth; exposure to environmental tobacco smoke (ETS); family history of adenotonsillectomy, otitis media and AR; and main polysomnography (PSG) data, were collected for univariate analysis. In addition, upper respiratory tract (oropharynx) conditional pathogen culture data were collected to analyze the relationship between the presence of conditional pathogens and the occurrence of OME in pediatric patients with OME.

The study design was approved by Beijing Tsinghua Changgung Hospital Ethics Committee (NO.: 22538-6-01, Nov. 8th, 2022). The minor(s)' legal guardian/next of kin consented to the collection of medical history, and examination and operation information.

2.2. Grouping criteria

The key points of diagnosis of OME were as follows: (1) ear symptoms and signs without acute middle ear infection; (2)

hearing loss, self-hearing enhancement, or hearing changes with posture changes occuring; (3) a tympanogram showed a "B" or "C" curve; (4) pure tone/behavioral audiometry indicating that the affected ear had mild to moderate conductive hearing loss; and (5) patients who showed tympanic effusion during the ear endoscopy before the operation which was confirmed intraoperatively. Patients diagnosed with OME according to the above criteria were included in the AH + OME group. Pediatric patients without OME were included in the AH group.

2.3. Criteria for collection of clinical data

Adenoid grading was based on endoscopic findings of the percentage of the posterior nostril blocked by the adenoid. Grades II–IV indicate a 26%–50%, 51%–75%, and ≥76% obstruction, respectively (10). Tonsil grading was performed according to Friedman's criteria. The tonsil grades include grade 0 (patients who have had their tonsils removed), grade 1 (the tonsils are inside the tonsillar fossa), grade 2 (the tonsils extend beyond the tonsillar pillars), grade 3 (the tonsils extend beyond the tonsillar pillars but do not reach the midline), and grade 4 (the tonsils extend as far as the midline (11). Tonsil hypertrophy was defined as tonsil grade II or higher. Regarding breastfeeding status, included children were those who were breastfed for more than six months after birth. Children in close contact with at least one active smoker (one or more cigarettes per day by any family member living with them) were considered to have ETS exposure (12). AR was diagnosed if a child showed excessive sneezing and at least one of the following symptoms: ocular pruritus, nasal pruritus, oropharyngeal pruritus, or clear nasal discharge (13). Preterm birth was defined as a gestational age of fewer than 37 weeks at the time of delivery. Family history was defined as the medical history of first-degree relatives. PSG monitoring data were collected, including obstructive apnea index (OAI) and apnea hypopnea index (AHI). An OAI > 1 time/h or AHI > 5 times/h for every nighttime sleep was considered abnormal (14). The severity of OSA was categorized as follows: mild, 5 times/h < AHI ≤10 times/h or 1 time/h < OAI ≤ 5 times/h; moderate, 10 times/h < AHI ≤ 20 times/h or 5 times/h < AHI ≤ 10 times/h; severe, AHI > 20 times/h or OAI > 10 times/h. Bacterial culture sampling was performed after general anesthesia and before surgery. For the collection of the samples, 0.9% sodium chloride solution was used to flush the oropharynx, and sterile pharyngeal swabs were used to swab the oropharynx repeatedly. The samples were then sent for bacterial culture. These strains were identified using MALDI-TOF MS (Bruker Dalton GmbH, Leipzig, Germany). The samples were cultured on Columbia agar supplemented with 5% sheep blood and Chocolate agar plates and incubated at 37°C for 48 h.

2.4. Statistical analysis

SAS Analysis Software (version 9.4, SAS Institute Inc, Cary, NC, USA) was used for data processing. $P < 0.05$ was considered to be statistically significant. The study was mainly divided into two parts for statistical and data analysis. Firstly, the influencing factors of the clinical data of AH complicated by OME were analyzed. Then the relationship between different pathogenic bacteria and AH complicated by OME was further analyzed based on a limited number of cases. In the process, the relevant clinical data of the AH group and AH + OME group were first analyzed by univariate analysis. Measurement data meeting the normality test and homogeneity analysis of variance were compared between the two groups by T-test; otherwise, Wilcoxon non-parametric test was used. Pearson's Chi-square test was used for enumeration data meeting the condition of the test; otherwise, a correction test or Fisher's exact test was used. Then, variables with $P < 0.1$ from the univariate analysis results were included in the multivariate logistic stepwise regression to screen out related factors affecting the pediatric patients with AH complicated by OME. In the analysis of correlation with pathogenic bacteria, the relevant pathogenic bacteria were screened out by univariate analysis. Furthermore, variables with $P < 0.05$ were taken as covariables, and the relationship between pathogenic bacteria and OME in pediatric patients with AH was further analyzed by multivariate logistic regression.

3. Results

3.1. Analysis of clinical data

A total of 511 pediatric patients with AH were included in this study. Of the 511 patients, 329 were boys, and 182 were girls. The age distribution of the patients was 5.37 ± 2.10 years. Regarding the two patient groups, 407 (79.6%) patients were included in the AH group, whereas 104 (20.4%) were included in the AH + OME group. Thirteen of the patients were missing PSG data owing to a lack of parental consent or lack of cooperation by the pediatric patients. Of the 498 patients with PSG data, 397 (79.7%) were in the AH group, and 101 (20.3%) were in the AH + OME group. The upper respiratory tract conditional pathogen culture data of 220 pediatric patients were collected. Of these, 178 (80.9%) were in the AH group, and 42 (19.1%) were in the AH + OME group.

Univariate analysis of the clinical data of the patients (**Table 1**) showed that there were statistically significant differences in age, BMI, adenoid grade, AR, breastfeeding status, and ETS between the AH and AH + OME groups ($P < 0.05$). The age distribution of the patients in the AH group was 5 (4–7) years, whereas that of those in the AH + OME group was 4 (4–5) years, and the difference between the two groups was statistically significant ($P < 0.0001$). The incidence of OME was higher in younger children and significantly higher in the 0–4 years age group than in the older age groups ($P = 0.0002$). The BMI (kg/m^2) of the pediatric patients in the AH group was higher than that of the patients in the AH + OME group ($P = 0.0030$). The incidence of OME among patients in the adenoid grade IV group was 26.86%, which was higher than that among patients in the grade III group (14.5%) ($P = 0.0005$). The incidence of OME among pediatric patients exposed to ETS was 36.72%, which was higher than that among patients who were not exposed to ETS (11.68%)

TABLE 1 Results of the univariate analysis of pediatric patients with adenoid hypertrophy with otitis media with effusion.

Variable	AH	AH + OME	χ^2	*P*-value
Sex			1.3379	0.2474
Male	257 (78.12)	72 (21.88)		
Female	150 (82.42)	32 (17.58)		
Age (years)	5 (4–7)	4 (4–5)	18.1938	<0.0001[b]
Age group (years)			16.7516	0.0002
0–4	164 (72.25)	63 (27.75)		
5–8	194 (83.62)	38 (16.38)		
9–12	49 (94.23)	3 (5.77)		
BMI	15.13 (13.96–16.9)	14.2 (13.66–16.21)	8.7825	0.0030[b]
Nasal congestion /rhinorrhea			0.2556	0.6132
No	67 (81.71)	15 (18.29)		
Yes	340 (79.25)	89 (20.75)		
Allergic rhinitis			6.9194	0.0085
No	227 (84.07)	43 (15.93)		
Yes	180 (74.69)	61 (25.31)		
Recurrent tonsillitis			0.0036	0.9523
No	283 (79.72)	72 (20.28)		
Yes	124 (79.49)	32 (20.51)		
Adenoid grade			12.0086	0.0005
III	230 (85.5)	39 (14.5)		
IV	177 (73.14)	65 (26.86)		
Tonsil grade			4.1044	0.3921
0	3 (60)	2 (40)		
1	31 (75.61)	10 (24.39)		
2	156 (77.23)	46 (22.77)		
3	164 (81.59)	37 (18.41)		
4	53 (85.48)	9 (14.52)		
Tonsil hypertrophy			2.7378	0.0980
No	190 (76.61)	58 (23.39)		
Yes	217 (82.51)	46 (17.49)		
History of adenoidectomy			0.0018	0.9666[a]
No	398 (79.76)	101 (20.24)		
Yes	9 (75)	3 (25)		
History of congenital diseases			0	1.0000[a]
No	399 (79.64)	102 (20.36)		
Yes	8 (80)	2 (20)		
Preterm birth			2.5011	0.1138
No	385 (80.38)	94 (19.62)		
Yes	22 (68.75)	10 (31.25)		
Breastfeeding			8.4788	0.0036
No	92 (70.77)	38 (29.23)		
Yes	315 (82.68)	66 (17.32)		
History of food/drug allergy			2.4518	0.1174
No	350 (80.83)	83 (19.17)		
Yes	57 (73.08)	21 (26.92)		
Family history of otitis media			0	1.0000[a]
No	389 (79.55)	100 (20.45)		
Yes	18 (81.82)	4 (18.18)		
Family history of adenotonsillectomy			0.2268	0.6339
No	381 (79.87)	96 (20.13)		
Yes	26 (76.47)	8 (23.53)		
Family history of allergic rhinitis			0.01274	0.9101
No	248 (79.49)	64 (20.51)		
Yes	159 (79.9)	40 (20.1)		
Environmental tobacco smoke			44.7721	<0.0001
No	295 (88.32)	39 (11.68)		
Yes	112 (63.28)	65 (36.72)		
AHI	3.8 (1.9–7.9)	4.6 (2.2–10.5)	1.1448	0.2846
OAI	0.1 (0–0.8)	0.2 (0–1.2)	1.5794	0.2088
OSA			2.2065	0.1374
No	233 (82.04)	51 (17.96)		
Yes	164 (76.64)	50 (23.36)		
Severity of OSA			4.0171	0.2596
No	233 (82.04)	51 (17.96)		
Mild	78 (78.79)	21 (21.21)		
Middle	53 (71.62)	21 (28.38)		
Severe	33 (80.49)	8 (19.51)		

Note: *t*-test was used for analysis of continuous variables, whereas Pearson's Chi-square test was used for analysis of categorical variables.
[a]Continuity-adjusted Chi-square test was used.
[b]Non-parametric test was used.
AH, adenoid hypertrophy; OME, otitis media with effusion; OAI, obstructive apnea index; AHI, apnea hypopnea index; OSA, obstructive sleep apnea.

($P < 0.0001$). The incidence of OME among breastfed pediatric patients was 17.32%, which was lower than that among those not breastfed (29.23%) ($P = 0.0036$). The incidence of OME among patients with AR was 25.31%, which was higher than that among those without AR (15.93%) ($P = 0.0085$). There were no statistically significant differences in sex, tonsil grade, comorbid nasal congestion/rhinorrhea, history of adenoidectomy, history of congenital diseases, preterm birth, history of food/drug allergy, family history of otitis media, adenotonsillectomy and AR, PSG monitoring results: AHI, OAI, and diagnosis and severity of OSA between the AH and AH + OME groups ($P > 0.05$).

The factors with a Pvalue <0.1 in the univariate analysis were included in the multivariate stepwise logistic regression analysis (Table 2). The results showed that age, adenoid grade, AR, breastfeeding status, and ETS exposure were important factors that influence the occurrence of OME in pediatric patients with AH. The results also showed that the risk of OME decreases with age. The patients in the 5–8 years [$P = 0.0062$, OR: 0.494 (0.299–0.819)] and 9–12 years [$P = 0.0055$, OR: 0.169 (0.048–0.592)] age groups had lower risks for OME than those in the 0–4 years group. The results also showed that a high adenoid grade was a risk factor for OME in pediatric patients with AH. The incidence of OME among patients in the adenoid grade IV group was 1.662 times than those in the grade III group [$P = 0.0438$, OR: 1.662 (1.014–2.723)]. ETS exposure was a risk factor for OME in pediatric patients with AH. Exposure to ETS increased the risk for OME by 4.839 times compared with non-exposure [$P < 0.0001$, OR: 4.839 (2.994–7.819)]. Children with AR were 1.906 times more likely to develop OME than those without AR

TABLE 2 Results of multivariate logistic regression analysis of pediatric patients with adenoid hypertrophy with otitis media with effusion.

Variable	Estimate	Standard Error	Wald χ^2	*P*-value	OR	OR (95% CI)	
Age group (years)							
0–4	Ref.						
5–8	−0.7042	0.2573	7.4909	0.0062	0.494	0.299	0.819
9–12	−1.7805	0.6407	7.7234	0.0055	0.169	0.048	0.592
Adenoid grade							
III	Ref.						
IV	0.5079	0.2519	4.065	0.0438	1.662	1.014	2.723
Allergic rhinitis							
No	Ref.						
Yes	0.645	0.2433	7.0289	0.008	1.906	1.183	3.071
Breastfeeding							
No	Ref.						
Yes	−0.6482	0.2599	6.2215	0.0126	0.523	0.314	0.870
Environmental tobacco smoke							
No	Ref.						
Yes	1.5766	0.2449	41.4469	<.0001	4.839	2.994	7.819

[$P = 0.008$, OR: 1.906 (1.183–3.071)]. Breastfeeding was a protective factor against OME in pediatric patients with AH [$P = 0.0126$, OR: 0.523 (0.314–0.870)].

3.2. Conditional pathogen culture analysis

The major pathogens identified in the upper respiratory tract (oropharynx) conditional pathogen culture analysis of the pediatric patients with AH included *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenzae* (**Table 3**). Univariate analysis showed that the incidence of OME was 22.97% in the conditional pathogen-positive group, which was higher than that in the conditional pathogen-negative group (11.11%) ($P = 0.0357$). The incidence of OME was 34.88% in the *S. pneumoniae*-positive group, which was higher than that in the *S. pneumoniae*-negative group (15.25%) ($P = 0.0033$). The incidence of OME was 33.33% in the *H. influenzae*-positive group, which was higher than that in the *H. influenzae*-negative group (16.84%) ($P = 0.0327$). The difference between the two groups was statistically significant ($P < 0.05$).

TABLE 3 Relationship between conditional pathogen culture and patients with adenoid hypertrophy with otitis media with effusion.

Variable	AH	AH + OME	χ^2	*P*-value
Conditional pathogen			4.4122	0.0357
No	64 (88.89)	8 (11.11)		
Yes	114 (77.03)	34 (22.97)		
Streptococcus pneumoniae			8.6300	0.0033
No	150 (84.75)	27 (15.25)		
Yes	28 (65.12)	15 (34.88)		
Staphylococcus aureus			3.6534	0.056
No	127 (77.91)	36 (22.09)		
Yes	51 (89.47)	6 (10.53)		
Moraxella catarrhalis			2.4219	0.1196
No	153 (82.7)	32 (17.3)		
Yes	25 (71.43)	10 (28.57)		
Haemophilus influenzae			4.5618	0.0327
No	158 (83.16)	32 (16.84)		
Yes	20 (66.67)	10 (33.33)		

The conditional pathogen culture analysis showed that age and adenoid grade were correlated with AH complicated by OME ($P < 0.05$) (**Supplementary Table S1**). Hence, after correcting for age and adenoid grade, the relationship between the presence of conditional pathogens and AH complicated by OME was analyzed (**Table 4**). Oropharyngeal *S. pneumoniae* positivity was found to be correlated with AH complicated by OME [$P = 0.0161$, OR: 2.647 (1.198–5.847)].

4. Discussion

OME is a major cause of hearing loss in children and can affect language and behavioral development (15). Epidemiological surveys have shown that more than 50% of children aged < 1 year and 60% of children aged <2 years have a history of OME (16). The high prevalence of OME among young patients is due to their incomplete structural and functional development of ET, which are affected by age-related ET factors, including length, angle, and closure capacity (17). In our study, age group analysis revealed that the proportion of pediatric patients with AH complicated by OME aged <4 years was higher than that of the other age groups. The results of the analysis also showed that the risk for OME decreased with increasing age. The difference between the two groups was statistically significant ($P < 0.05$). There is no consensus on the relationship between gender and OME. The disease is expected to be more common in boys as mastoid pneumatization is more rapid in girls and boys experience upper respiratory infection episodes more frequently. Some studies also showed that OME is more common in males (18). On the contrary, other studies showed no relationship between sex and the prevalence of OME (19–21). In our study,

TABLE 4 Relationship between conditional pathogen culture and adenoid hypertrophy with otitis media with effusion (corrected for age and adenoid grade).

Variable	Estimate	Standard Error	Wald χ^2	*P*-value	OR	OR (95% CI)	
Conditional pathogen							
No	Ref.						
Yes	0.5858	0.4428	1.7505	0.1858	1.796	0.754	4.279
Streptococcus pneumoniae							
No	Ref.						
Yes	0.9735	0.4043	5.797	0.0161	2.647	1.198	5.847
Hemophilus influenzae							
No	Ref.						
Yes	0.8834	0.4648	3.6123	0.0574	2.419	0.973	6.016

there was no statistical difference in sex distribution between the AH and AH + OME groups ($P = 0.2475$).

AH is the main cause of ETD, and OME is associated with ETD (10, 22). One study showed that 29.2% of children with adenoid enlargement had a co-morbidity of asymptomatic OME (23). The etiology of OME mainly includes anatomical, immune, microbiological, and environmental factors (6); however, its etiology is not completely clear. Hence, there is a need to examine the mechanisms and factors that influence AH complicated by OME. It is necessary to fully understand the risk factors related to OME incidence in pediatric patients with AH to better screen for and manage this disease. Our study fully collected various data from the etiology and mechanism. A comprehensive and in-depth analysis of these factors early can facilitate appropriate, timely intervention, thereby preventing disease progression. It provides a reference for the prevention and treatment of diseases. It also provides a basis and ideas for researching the deep mechanism and correlation of each influencing factor.

4.1. Mechanical obstruction

Hypertrophic adenoids, particularly tissues near the torus and pharyngeal opening of the ET, can directly compress and obstruct the ET, resulting in impaired middle ear drainage, negative middle ear pressure, mucosal exudation, and OME. Studies have shown that the degree of AH is significantly correlated with OME and that the greater the degree, the higher the incidence of OME. In addition, OME tends to persist, and conservative treatment tends to fail in cases of higher degrees of AH. Children with a higher grade of AH have a higher risk of OME persistence, leading to conservative treatment failure and requiring surgical intervention, but this study had a limited sample size of only 65 cases (24). The present study showed that the incidence of OME in the adenoid grade IV group was 26.86%, which was significantly higher than that in the grade III group (14.5%) ($P = 0.0005$). The incidence of OME in the adenoid grade IV group was 1.662 (1.014–2.723) times than that in the grade III group. A high adenoid grade is a risk factor for AH complicated by OME. The higher the adenoid grade, the greater the respiratory tract obstruction and the more severe the OSA in pediatric patients (25). However, PSG monitoring data analysis in this study revealed no significant correlation between the AHI, OAI, diagnosis and severity of OSA, and the incidence of OME in pediatric patients with AH ($P > 0.05$). This might be due to the population distribution in the present study and multiple potential factors. Further in-depth studies are required to clarify the relationship between these variables and the incidence of OME. Regardless, clinicians should be vigilant in managing pediatric patients with AH and OME who present with OSA. Timely screening and intervention should be performed in such cases.

4.2. Pathogenic microorganisms

OME may be a sequela of acute otitis media (AOM). OME tends to occur in cases of AH and ETD; however, the middle ear environment determines the occurrence of OME (26). The upper respiratory tract is an important region for the occurrence of otitis media. According to the pathogen reservoir theory, long-term retention of pathogen-carrying secretions in hypertrophic adenoid crypts can become a microorganism "reservoir". Pathogens can reach the middle ear through the ET, causing disease. Bacteria detected in adenoid tests include normal bacteria and conditional pathogens in the nasopharynx. Conditional pathogens mainly include *S. pneumoniae*, *H. influenzae*, *S. aureus*, and *M. catarrhalis*. These pathogens can cause otitis media, nasal sinusitis, upper respiratory tract infections, pneumonia, and systemic diseases (26–30). Typical ear pathogens isolated from middle ear effusions, nasopharyngeal samples, and adenoid samples include *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*. In addition, multi-pathogen infections are often present in OME (31, 32). After viral infection of the upper respiratory tract occurs, the pathogens can ascend to the middle ear through the ET (33) and disrupt the respiratory tract flora. Viruses can cause bacteria to transform from commensal to pathogenic, disrupt the airway epithelial barrier, decrease mucus and cilia clearance, induce the host to provide nutrients to pathogens, and promote adhesion and virulence in ear pathogens (34). Oropharyngeal and nasopharyngeal pathogens in children tend to translocate to the middle ear owing to the structural characteristics of the ET and the middle ear negative pressure caused by AH (35). Some

studies have compared the bacteriology of the adenoids and tonsils in children by culture, and found an overall similarity in the bacteria sampled from the surfaces of tonsils and adenoids of children (36, 37). Surface samples from the nasopharynx and oropharynx may easily be contaminated by saliva, tears, and other secretions. Other studies used 16S rRNA gene pyrosequencing. One study found that the microbiome differs between crypts of the adenoids and crypts of the tonsils, including the relative abundances of potential pathogens such as *H. influenzae*, *S. pneumoniae,* and *M. catarrhalis* (38). Another study has reported combined analyses of the adenoids and tonsils microbiome in pediatric. The microbiome was not significantly different at the phylum level between the adenoids and tonsils (39). In future studies, 16S rRNA gene pyrosequencing technology can be used to identify the differences in bacterial distribution. In addition, whole-genome sequencing should be conducted to analyze the specificity of bacterial capsules and virulence factors. In our study, conditional pathogen culture analysis of the oropharynx which represented the upper respiratory tract revealed that the conditional pathogens detected in the oropharynx of the pediatric patients mainly consisted of *S. aureus*, *S. pneumoniae*, *M. catarrhalis*, and *H. influenzae*. The results of the univariate analysis (**Table 3**) showed that the incidence of OME was higher in the conditional pathogen-positive group, *S. pneumoniae*-positive group, and *H. influenzae*-positive group than in the corresponding negative groups; the inter-group differences were statistically significant ($P < 0.05$). In addition, there were statistically significant differences in age and adenoid grade between the groups ($P < 0.05$) (**Supplementary Table S1**). After correcting for the effects of age and adenoid grade on the incidence of OME, the results showed that presence of *S. pneumoniae* in the oropharynx is a risk factor for the occurrence of OME in pediatric patients with AH. The incidence of OME in the *S. pneumoniae*-positive group was 2.647 times that in the *S. pneumoniae*-negative group [$P = 0.0161$, OR: 2.647 (1.198–5.847)] (**Table 4**). Future studies with larger sample sizes are needed for further analysis of these results.

4.3. Local immune dysregulation in adenoids and allergic reactions

The middle ear is an independent immune organ that is structurally connected to the ET and the upper respiratory tract. Based on the same airway principle, antigens that stimulate the nasal mucosa can also produce mucosal immune responses in the ET and the middle ear. Adenoids contain T and B lymphocytes in different developmental stages and are major secondary lymphoid organs that constitute Waldeyer's ring. They participate in innate and acquired immunity to resist upper respiratory tract infections in children. Local immune dysregulation decreases adenoid barrier function and increases the incidence of host OME. There are differences in adenoid lymphocyte subset distribution in pediatric patients with AH. Patients with AH + OME show higher T and B lymphocyte counts than those with AH only, which leads to increased local antigen-presenting dendritic cell count (40), increased capture of airway pathogens, decreased immune function, and increased host susceptibility. Immunoglobulins produced by B cells are an important defense mechanism against otitis media and other upper respiratory tract infections (41). The present study showed that AR increases the risk for OME in pediatric patients with AH. AR is an IgE-mediated type I hypersensitivity reaction that is characterized by increased vascular permeability, increased mast cells and related inflammatory cell secretion of histamine, leukotriene, and other inflammatory mediators, occurrence of mucosal edema and exudation, obstruction of the ET, and decreased cilia motility, resulting in OME. Allergies contribute to the occurrence and progression of AH and OME. The incidence of OME is significantly higher in pediatric patients with AR than in pediatric patients without AR (42, 43). However, the specific incidence of OME is determined by population characteristics and diagnostic criteria. A systematic review of the pathophysiology by which allergy increases the risk of otitis media showed that allergy is related to the occurrence and acute exacerbation of OME (44). Allergen stimulation causes local immune responses, elevated Th2 cytokine secretion, weakened upper respiratory tract mucosal barrier function, increased nasopharyngeal bacteria (45), and increased incidence of OME. IgE, IL-4, histamine, and eosinophil levels in middle ear effusions are increased in patients with OME. In patients with AR, IL-4, IL-5, IFN-γ, and histamine secretions in the nasal mucosa are increased (46). In a previous study of a mouse model of OME created by inducing middle ear infection, middle ear mucosal immune responses towards bacterial lipopolysaccharides were increased in the AR group (47).

Besides etiological factors, several immutable factors such as genetic factors and family history, and variable factors such as environment and lifestyle can affect the occurrence and progression of the disease (48). ETS exposure is also known as "secondhand smoking" or "passive smoking". Animal studies have demonstrated that nicotine can stimulate the hypothalamus $\alpha 3\beta 4$ nicotinic acetylcholine receptor to decrease appetite, energy intake, and body weight (49). Parental smoking is a common source of ETS exposure in children. Interventional measures should be employed to decrease ETS exposure in children and improve their health (50, 51). In the United States, 29.2% of adolescents are exposed to ETS (52).Thus, protocols for improving home-smoking behavior should be studied and implemented (53). ETS exposure and AR in children are associated with increased prevalence of eczema (54). Studies have shown that passive smoking and ETS exposure are environmental risk factors for OME in children (20, 55). Maternal smoking habits and the number of family members who are smokers are significantly correlated with the risk of otitis media in children aged < 4 years old (56). However, some studies did not show an association between ETS exposure and otitis media in children (19). Our study showed that ETS exposure is a risk factor for the occurrence of OME in pediatric patients with AH. The main harmful components of cigarettes, including nicotine, tar, carbon monoxide, and acrolein, can cause

respiratory diseases (57) and destroy ET surfactants. Cilia toxins decrease ciliary beat frequency and cause the ET mucosa and cilia in children to be susceptible to damage. Thus, adult smoking can disrupt upper respiratory tract flora (58) and affect children.

Our study showed that the incidence of OME in breastfed pediatric patients was 17.32%, which was lower than that in the patients who were not (29.23%) ($P = 0.0036$). This indicates that breastfeeding is a protective factor against the occurrence of OME in pediatric patients with AH (**Table 2**). Breast milk not only contains antibacterial substances, but can also promote the development of healthy flora and is negatively correlated with respiratory tract infections (59, 60). In addition, breast milk can optimize immune function and decrease the risk of otitis media and respiratory tract infections in infants and toddlers (61–63). A Lancet paper analyzed the potential mechanisms underlying the effects of breastfeeding in terms of immunology, epigenetics, microbiomics, and stem cell research. Increased breastfeeding can decrease rate of mortality in children and prevent infectious diseases. In addition, the protective effects of breastfeeding against otitis media in children can extend up to age 2 and older (64). In addition to providing environmental pathogen-specific IgA, breast milk can develop non-specific defenses against bacterial pathogens. Besides preventing upper respiratory tract infections, maternal antibodies can also act on middle ear pathogens and interfere with bacterial adhesion to the nasopharyngeal epithelium to prevent acute otitis media (65). Antigen stimulation can result in the production of IgG antibodies against non-typeable *H. influenzae* (66) and regulate an infant's humoral immune responses towards common OME pathogens. Milk bottle suction and the swallowing pressure gradient can cause ETD and increase susceptibility to otitis media (67).

In summary, the pathogenesis of AH with OME is complex and is influenced by many factors. Younger age and a high adenoid grade are major risk factors for the occurrence of OME in pediatric patients with AH. ETS exposure, a non-breastfed status, AR, and presence of conditional pathogens (mainly *S. pneumoniae*) in the upper respiratory tract also influence the pathogenesis of AH complicated by OME. This study provides a foundation and basis for future etiological mechanism studies and treatments. It is necessary to study deep mechanisms and correlations in the future, such as the establishment of animal models related to the incidence of OME influencing factors and whole-genome sequencing for the analysis of the specificity of bacterial capsules and virulence factors.

The presented study still had some main limitations. The sample sizes were limited, especially the cases of conditioned pathogen culture. In addition, the study time range included the global COVID-19 pandemic, which involved Beijing's strict implementation of the dynamic zero-COVID policy during this period. The prevalence of the novel coronavirus did not affect the incidence and progression of the disease in the study population. However, the overall number of patients hospitalized for AH and related diseases decreased compared to before the epidemic. In particular, there were very few patients from other cities, which seemed to have a potentially unavoidable effect on the distribution of the study population.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Beijing Tsinghua Changgung Hospital Ethics Committee. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

CWJ collected data, statistical analysis, and wrote the article. YGP revised the manuscript. CYJ, WYY, ZCM, and WW participated in data collection. WLJ proposed ideas for the experiment. YJY helped with study design and project administration. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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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Supplementary material

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Inflammatory markers in children with obstructive sleep apnea syndrome

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Objective: To evaluate serum inflammatory markers of YKL-40, Interleukin-6 (IL-6), Interleukin-8(IL-8), Interleukin-10(IL-10), TNF-α(tumor necrosis factor-α), and CRP (C-reactive protein) in children with and without OSAS.
Methods: The ELISA technique has been used to identify the concentration of inflammatory markers such as YKL-40, IL-6, IL-8, IL-10, TNF-α, and CRP in the serum of 83 children with OSAS and 83 children without OSAS.
Results: Serum levels of YKL-40, IL-6, IL-8, and IL-10 were found to be increased in children with OSAS. YKL-40 was found to be positively correlated with IL-6 and IL-8, and negatively correlated with IL-10. At the same time,YKL-40 was also found to be positively correlated with OAHI and LoSpO2% in OSAS group. IL-8 was positively correlated with OAHI whereas IL-10 was positively correlated with LoSpO2.
Conclusion: Children with OSAS are in a systemic inflammatory state. YKL-40 together with IL-8 may act as serum inflammatory markers and provide an indication for the diagnosis of children with OSAS.

KEYWORDS

YKL-40, inflammatory factors, interleukin, OSA (Obstructive sleep apnea), obstructive sleep apnea syndrome

1. Introduction

Obstructive sleep apnea syndrome (OSAS) has become one of the common diseases affecting 1.2% to 5.7% of children. Symptoms of pediatric OSAS include habitual sleep snoring, mouth breathing, repeated awakening, enuresis, excessive sweating, hyperactivity, and so on (1, 2). Severe OSAS causes associated complications such as growth retardation, cardiovascular disease, neurocognitive abnormalities, behavioral problems, and even causes craniofacial malformations and thoracic deformity (3, 4). Studies showed that children with OSAS caused greater burdens on family finance and quality of life than children without OSAS at all ages (5).

At present, polysomnography (PSG) is still the gold standard for diagnosing OSAS in children. Due to poor coordination, some snoring children cannot be successfully diagnosed as OSAS by PSG. To simplify the diagnosis of pediatric OSAS, there is a great necessity to identify serum biomarkers which can be used as surrogates of PSG. A growing number of studies depict that pediatric OSAS is associated with a systemic inflammatory response. Inflammatory markers such as IL-6, IL-8, CRP, TNF-α, INF-γ, ICAM, and VCAM have been found to increase in children with OSAS in accordance

with different reports (6–9). However, there are no specific serum biological markers available for the diagnosis of OSAS. In recent years, we have focused on an inflammatory factor, YKL-40, which is involved in other inflammatory diseases and can promote the elevation of some cytokines. YKL-40 has not been reported in pediatric OSAS so far. This study is to verify the systemic inflammation in children with OSAS and explore the specific inflammatory markers for pediatric OSAS.

2. Materials and methods

A total of 83 children aged from 2 to 14 years old who underwent adenotonsillectomy (ATE) for OSAS were recruited in our hospital from 2020 July to 2021 February.The diagnosis of OSAS was confirmed by PSG. The children were monitored at night for at least 7 h in a quiet and comfortable state by Alice 5 Philips sleep monitors. Physiologic parameters included finger oxygen saturation, nose and mouth airflow, respiratory effort, snoring, sleep stages, body position, and heart rhythm. The data was processed by computers and manually corrected by professional technicians. The criteria for pediatric OSAS was according to Chinese guideline for the diagnosis and treatment of childhood obstructive sleep apnea (2). Mild OSAS is obstructive apnea hypopnea index (OAHI) between 1 and 5 events per hour, moderate OSAS is OAHI >5 to ≤10 events per hour, and severe OSAS is OAHI greater than 10 events per hour. We screened 83 children by OSA-18 questionnaire and those with a score of below 19 (10) in their physical examination in our hospital were recruited as the control group according to 1:1 of matched age and gender during the same period. The research was approved by an Ethics Committee (IEC-FOM-013-1.0). Informed consent was obtained from the participants and their guardians when the serum was collected. Exclusion criteria were acute inflammation; respiratory tract infection or asthma; cardiac disease and obesity.

3. ELISA of inflammatory markers

Fasting peripheral blood samples of 2 ml were drawn from all children after awakening in the morning. The supernatant was taken by centrifugation at 3,000 r/min and stored in a frozen depository marked tube under −80°C temperature. The inflammatory mediators' concentrations of YKL-40, IL-6, IL-10, IL-8, TNF-α, and CRP were determined by ELISA kits (Invitrogen United States) according to the manufacturer's protocol. The sensitivity of YKL-40, IL-6, IL-8, IL-10, TNF-α, and CRP were 10.83 pg/ml;0.92 pg/ml; ≤5 pg/ml; 1.0% pg/ml; 2.3 pg/ml and ≤10 pg/ml respectively. Optical density at 450 nm was determined using an Auto-Reader Model (SpectraMax i3x, MD, CA).

4. Statistical analysis

Data are expressed using mean ± standard deviation or median and interquartile spacing. Statistical analyses is performed using the GraphPad Prism (version 7) statistical software. χ^2 tests are used to compare categorical variables in different groups. Wilcoxon or Kruskal-Wallis rank sum tests are used to analyze significant differences between groups. Spearman rank correlation or Pearson is used to analyze the correlation. P value <0.05 is considered statistically significant.

5. Results

5.1. Demographic characteristics of children at baseline

A total of 83 children with OSAS which includes [54 (65%)] boys and [29 (35%)] girls with a mean age of 7.0 ± 2.7 years old compared with 83 children without OSAS including the same percentage of boys and girls with a mean age of 6.8 ± 3.5 years. The children's characteristics in the three subgroups categorized by OSAS severity at baseline are shown in **Table 1**. There was no significant difference in age and BMI between OSAS and control groups. There was no significant difference in the course of the disease, tonsil size, and adenoids' size among the three subgroups. Significant differences in OAHI and LoSaO2% were noted among the three subgroups of pediatric OSAS.

TABLE 1 Demographic characteristics in children at baseline.

Characteristic	OSAS ($n = 83$)	Normal ($n = 83$)	*P*-value	Mild-OSAS ($n = 53$)	Moderate-OSAS ($n = 11$)	Severe-OSAS ($n = 19$)	*P*-value
Age (Year)	7 ± 2.7	6.8 ± 3.5	0.425	6.9 ± 2.5	7.6 ± 2.8	6.8 ± 3.2	0.631
Sex (Male/Female)	54/29	54/29	–	31/22	7/4	16/3	0.130
BMI (kg/m^2)	17.1 ± 3.3	16.9 ± 3.4	0.656	16.5 ± 3.0	17.7 ± 3.6	18.2 ± 3.8	0.306
Course of disease (Month)	27.5 ± 29.1	–	–	28.9 ± 29.8	29.2 ± 35.3	22.6 ± 23.8	0.740
Tonsils size (I/II/III)	8/39/36	–	–	4/24/25	2/7/2	2/8/9	0.358
Adenoid size (A/N)	0.7 ± 0.1	–	–	0.7 ± 0.1	0.7 ± 0.1	0.7 ± 0.1	0.527
OAHI	7.9 ± 8.4	–	–	3.8 ± 2.4	5.6 ± 4.0	13.5 ± 11.0	**<0.001**
LoSpO2%	89.6 ± 4.5	–	–	91.4 ± 3.2	89.9 ± 2.0	84.3. ± 5.3	**<0.001**

Age, Year; Sex, Male/Female; BMI, body mass index; Course of disease, Month; Tonsils size: Degree of I–IV; Normal: control group; OAHI, obstructive apnea hypopnea index; LoSpO2%, lowest oxyhemoglobin saturation by pulse oximetry.
The bold value indicates a statistical significance.

5.2. Inflammatory markers in children with and without OSAS

The levels of YKL-40, IL-6, IL-8, and IL-10 in the serum of children were higher in the OSAS group than in the control group, and a significant difference ($P < 0.05$) was noted between the two groups. The levels of CRP and TNF-α were higher in OSAS than in the control group, but there was no significant difference ($P > 0.05$) between the two groups (Table 2).

5.3. Inflammatory markers in subgroups of OSAS

Serum levels of YKL-40 were higher in the severe than moderate OSAS group and moderate OSAS than mild OSAS group. But there was no significant difference among the three groups ($P > 0.05$). There was no significant difference in the levels of IL-8, IL-10, and TNF-α among the three groups ($P > 0.05$). The level of IL-6 was highest in the moderate group and a significant difference was noted among the three groups ($P < 0.05$). The level of CRP was highest in the severe group compared with the mild and moderate OSAS groups ($P < 0.05$) (Table 3). Combine moderate and severe OSAS, Serum levels of YKL-40 and IL-8 was found statistical differences between mild and moderate-severe groups (Figure 1).

TABLE 2 Inflammatory markers in children with and without OSAS.

	OSAS ($n = 83$)		Normal ($n = 83$)		*P*-value
	M	P_{25}–P_{75}	M	P_{25}–P_{75}	
YKL-40 (ng/ml)	29.28	22.98–39.32	25.13	20.79–32.84	**0.027**
CRP (mg/L)	0.19	0–1.39	0.03	0.01–0.31	0.566
IL-6 (pg/ml)	1.91	0–2.63	0.00	0–1.73	**0.002**
TNF-α (pg/ml)	830.22	616.20–996.52	813.46	626.5–975.72	0.761
IL-8 (pg/ml)	66.65	40.19–121.42	28.29	15.21–56.79	**<0.001**
IL-10 (pg/ml)	7.075	2.48–12.79	4.86	0–8.53	**0.008**

M, median (IQR); P_{25}–P_{75}, M (P25, P75).
The bold value indicates a statistical significance.

5.4. Correlation between the inflammatory factors and the baseline data in OSAS

YKL-40 was positively correlated with OAHI and LoSpO2% in OSAS group ($P < 0.05$). CRP was positively correlated with adenoid size. IL-8 was found to be positively correlated with OAHI in the OSAS group ($P < 0.05$) whereasIL-10 was positively correlated with LoSpO2% ($P < 0.01$) (Table 4, Figure 3).

5.5. Correlation among the inflammatory factors

In OSAS group, the correlation among the inflammatory factors was analysed.

YKL-40 was positively correlated with IL-6 and IL-8 ($P < 0.05$). YKL-40 was negatively correlated with IL-10 ($P < 0.05$). There were no correlations between IL-6 and IL-8, IL-6 and IL-10, IL-8 and IL-10 ($P > 0.05$) (Figure 2).

5.6. ROC curves of the inflammatory markers for OSAS

In order to evaluate the predictive value of these inflammatory markers for OSAS, YKL-40, IL-6, IL-8, and IL-10 which had significant differences between OSAS and control group were selected to operate characteristic ROC (receiver operating characteristic) curve. AUC (Area Under Curve) was used for the evaluation of diagnostic tests and AUC >0.5 can be used as a valid diagnosis (Figure 3). Cut-off values are shown in Table 5.

6. Discussion

Chronic persistent mild inflammation has become the most likely pathogenesis factor to cause OSAS (6), and the degree of the inflammatory response is correlated with the severity of OSAS (9). Among the inflammatory markers in pediatric OSAS, serum concentrations of IL-6, IL-8, IL-10, TNF-α, and CRP were the most frequently reported, but the association of these inflammatory factors with OSAS varied in different studies.

TABLE 3 Inflammatory markers in subgroups of OSAS.

Characteristic	Mild-OSAS ($n = 53$)		Moderate-OSAS ($n = 11$)		Severe-OSAS ($n = 19$)		*P*-value
	M	P_{25}–P_{75}	M	P_{25}–P_{75}	M	P_{25}–P_{75}	
YKL-40(ng/ml)	28.41	22.77–36.44	31.53	27.37–36.97	37.87	23.85–44.4	0.267
CRP (mg/l)	0.00	0.00–1.01	1.13	0.19–1.52	1.30	0.16–1.72	**<0.001**
IL-6(pg/ml)	0.435	0.00–2.17	2.63	2.05–3.38	2.24	1.74–2.61	**<0.001**
TNF-α (pg/ml)	857.77	693.7–985.58	775.92	93.17–1,058.51	1,032.69	899.63–1,121.34	0.053
IL-8 (pg/ml)	68.22	42.405–115.12	54.14	28.87–113.99	71.51	45.27–148.06	0.757
IL-10 (pg/ml)	8.36	3.36–12.55	6.57	1.99–15.12	5.75	0–13.98	0.872

M, median (IQR); P_{25}–P_{75}, M (P25,P75).
The bold value indicates a statistical significance.

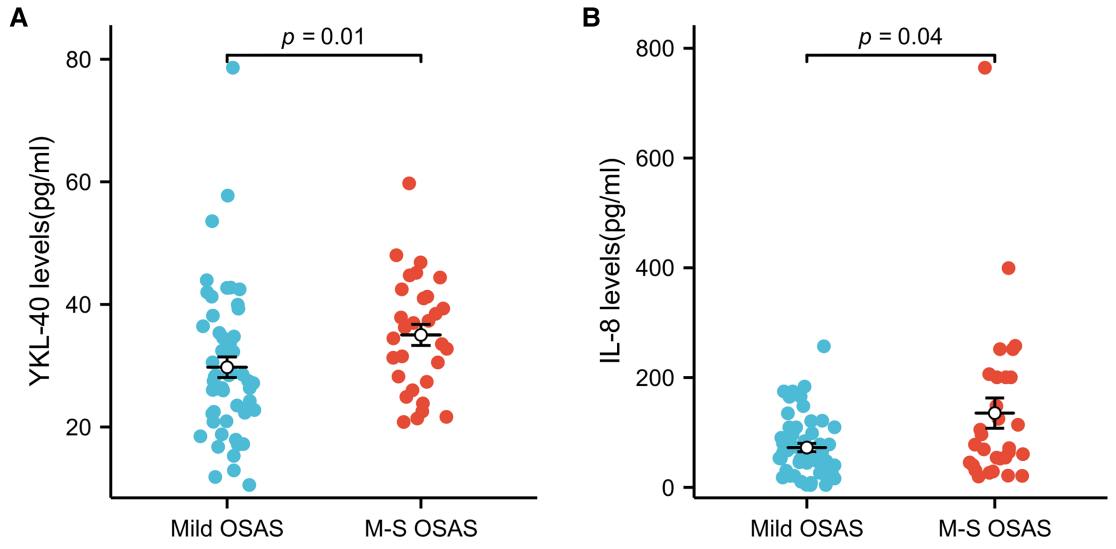

FIGURE 1
YKL-40 and IL-8 level in subgroups of OSAS. (A) Serum levels of YKL-40 in mild OSAS and moderate and severe groups (B) serum levels of IL-8 in mild OSAS and moderate and severe groups.

TABLE 4 Correlation between the inflammatory factors and the baseline data.

	Course of disease (Month)	Tonsils size (I/II/III)	Adenoid size (A/N)	OAHI	LoSpO2
	P-value	*P*-value	*P*-value	*P*-value	*P*-value
YKL-40	0.465	0.622	0.632	**0.038 ($r = 0.295$)**	**0.018 ($r = -0.33$)**
CRP	0.594	0.566	0.154	0.107	0.066
IL-6	0.607	0.154	0.993	0.619	0.481
TNF-α	0.878	0.751	0.614	0.287	0.629
IL-8	0.051	0.770	0.296	**0.043 ($r = 0.287$)**	0.299
IL-10	0.431	0.350	0.382	0.353	**0.006 ($r = 0.289$)**

OAHI, obstructive apnea hypopnea index; LoSpO2%, lowest oxyhemoglobin saturation by pulse oximetry.
The bold value indicates a statistical significance.

Our results suggest that the levels of IL-6, IL-8, and IL-10 in the serum of children were higher in OSAS than in the control group, but the levels of TNF-α and CRP had no significant difference in the two groups. Our results were consistent with the study of Albert M Li et al. (9). They found children with OSAS had higher serum IL-6 and IL-8, but TNF-α had no difference between children with and without OSAS. In Tam's study, serum levels of IL-8 were elevated, but IL-6, IL-10, TNF-α, and CRP had no change in children with and without OSAS. Higher IL-6 and lower cytokine IL-10 in non-obese children with OSAS were reported in Gozal's study (6). These differences may be caused by different races, age distribution, the severity of OSAS, and different selection of the control group. In our study, the control group was composed of healthy children without sleep-related symptoms, but in other studies, the control group was selected by children with habitual snoring.

YKL-40 is a proinflammatory factor, which is secreted by macrophages, neutrophils, fibroblasts, hepatic stellate cells, endothelial cells, and epithelial cells. YKL-40 maintains the homeostasis of various organs and participates in inflammatory reactions (11). YKL-40 has been reported enhanced in adult OSAS, and its level was correlated with apnea-hypopnea index (AHI) in adults with OSAS (12, 13).

We found elevated YKL-40 levels in children with OSAS compared to the healthy control group. Moreover, in the study of subgroups, serum YKL-40 levels were higher in the severe than the moderate OSAS group and in the moderate than the mild OSAS group, but there was no significant difference among the three groups. The results were different from L.C. MUTLU's report in adults with OSAS. Maybe the uneven case distribution of patients and mild OSAS was predominant among the three groups, which has caused no significant difference in YKL-40 levels among the three groups.

When we combined moderate and severe, there were statistical differences between mild and moderate-severe groups. Positive correlation was noted between YKL-40 and OAHI, as well as between YKL-40 and LoSpO2 in our study. This demonstrates YKL-40 may be used as a potential possible biomarker for screening pediatric OSAS and an indicator of OSAS severity. This is the first report about serum YKL-40 levels in pediatric OSAS. The relationship between YKL-40 and OSAS needs further studies *in vitro* and *in vivo*.

In the study of IL-6, IL-8, IL-10, TNF-α, and CRP in subgroups of pediatric OSAS, IL-6 and CRP were foundto have significant differences among the three groups. We found the level of IL-6 was highest in the moderate group.Combined with clinical knowledge, this result may not be clinically significant. The bias which can occur in the result could be due to the uneven distribution of disease severity.

IL-6 is a proinflammatory cytokine and an initiator of the inflammatory response. Serum and plasma interleukin-6 levels

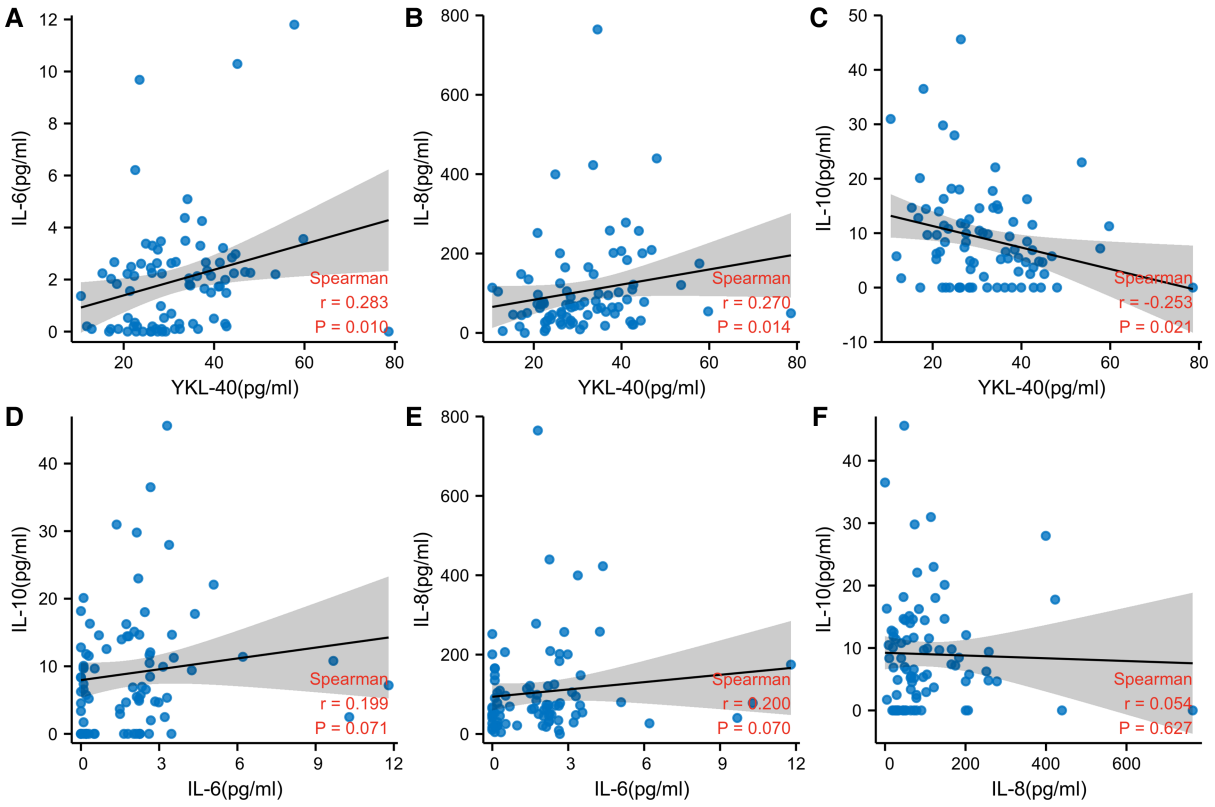

FIGURE 2
Correlation between the inflammatory factors. (A) Spearman correlation between YKL-40 and IL-6 (B) spearman correlation between YKL-40 and IL-8 (C) spearman correlation between YKL-40 and IL-10 (D) spearman correlation between IL-6 and IL-10 (E) spearman correlation between IL-6 and IL-8 (F) spearman correlation between IL-8 and IL-10. (weak correlation: $0.1 < r < 0.3$, moderate correlation: $0.3 < r < 0.5$, strong correlation: $0.5 < r < 1.0$).

were higher in OSAS compared to healthy controls (14). Under the condition of inflammation caused by injury, IL-6 is secreted by T cells and macrophages in the tonsils and induces the activation, proliferation, and differentiation of T cells to participate in the immune response of the body (15). Therefore, it is speculated that intermittent hypoxia in children with OSAS may cause cell damage in tissues and promote the secretion of IL-6 by T cells and macrophages.

CRP was also found to show a significant difference among the three groups. The finding was also consistent with many reports which has published previously (16–18).

The expression of CRP was IL-6 dependent and greatly regulated by IL-6 (18, 19). But we found no significant difference in CRP between the OSAS group and the control group nor a correlation between CRP and IL-6 in this study. Therefore, the expression and interaction of inflammatory factors in OSAS are

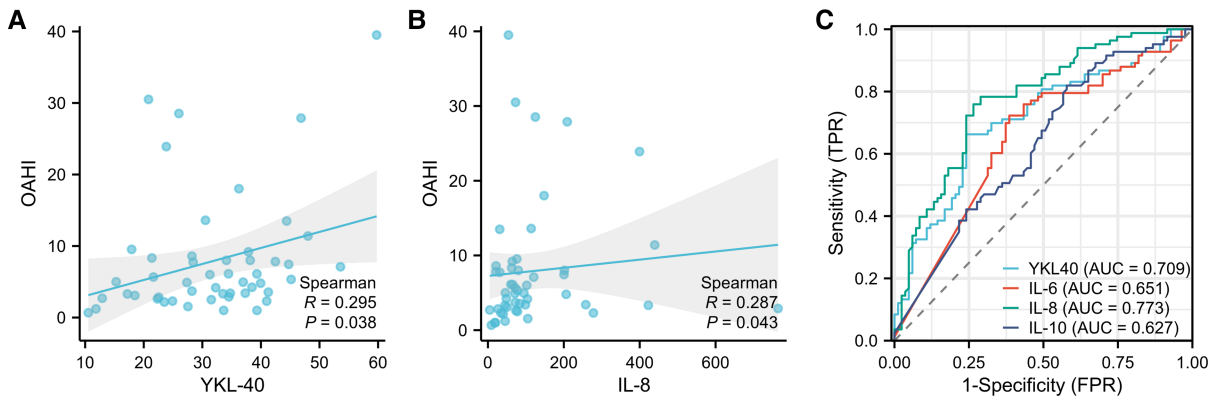

FIGURE 3
Correlation between YKL-40, IL-8, and OAHI, ROC curves of the inflammatory markers for OSAS. (A) Correlation between YKL-40 and OAHI (B) correlation between IL-8 and OAHI (C) area Under Curve (AUC) of YKL-40, IL-6, IL08, IL-10. (0.5–0.7 AUC shows low accuracy, 0.7–0.9 AUC shows accuracy, and above 0.9 AUC shows high accuracy).

TABLE 5 Information of ROC.

	Cut-off value	Sensitivity	Specificity	Precision	Positive predictive value
YKL40	25.78	0.66	0.76	0.71	0.733
IL-6	1.49	0.72	0.62	0.67	0.652
IL-8	45.65	0.78	0.71	0.75	0.730
IL-10	9.60	0.82	0.42	0.62	0.586

more complex than those reported in the literature and studies at present IL-8, IL-10, and TNF-α had no differences in the subgroups. When the OSAS group was divided into two groups, IL-8 had a significant difference between the mild and moderate-severe groups. IL-8 was positively correlated with OAHI. So, IL-8 may be used as a marker for the prediction of OSAS severity.

On the correlation among other inflammatory factors, significant positive correlations were noted between YKL-40 and IL-6, YKL-40, and IL-8. Anegative correlation was noted between YKL-40 and IL-10. The increase of circulating YKL-40, IL-6, IL-8, and IL-10 and the association between YKL-40 and IL-6, IL-8, and IL-10 has been reported separately in different inflammatory diseases. In 2011, Anders R. Nielsen demonstrated that IL-6 had a key role in the regulation of plasma YKL-40 levels during inflammation (20). In 2014, Tuija Väänänen reported that the levels of YKL-40 were higher andits concentration was correlated positively with IL-6 in osteoarthritis (21). The relation between YKL-40 and IL-8 was reported in colitis-associated neoplasia (22) and asthma (23). The demonstrated YKL-40 has enhanced the secretion of IL-8 under inflammatory conditions and could be a useful biomarker for patients with neoplasia and asthma. In 2012, Appleby LJ reported CHI3L1 level was elevated and negatively associated with IL-10 in Schistosoma haematobium-infected children (24).

The associations among IL-6, IL-8, and IL-10 were were found to be differently depicted in different publishes. We could not find the exact correlations between IL-6 and IL-8, IL-6 and IL-10, and IL-8 and IL-10 in pediatric OSAS. This may be due to the existence of different control groups, different races, different age distribution, different disease severity, and so on. The correlation, interaction, and mechanism of inflammatory factors need to be thoroughly studied in the future.

Recently, a case-control study showed that osteoprotegerin, chitinase 3-like protein 1(YKL-40, AUC = 0.9734), and cardiotrophin-1 could be used as potential biomarkers of OSA in adults (25). The ROC curve analysis performed for the serum levels of YKL-40, IL-6, IL-8, and IL-10 in our study. The result showed YKL-40 and IL-8 (AUC > 0.7) had more accurate predictive capabilities for pediatric OSAS compared to IL-6 and IL-10 (AUC < 0.7). The cut-off value of serum levels of YKL-40 is 25.78 and IL-8 is 45.65. For pediatric OSAS prediction as a screening test, the concentrations of YKL-40 (>25.78 pg/ml) and/or IL-8 (>45.65 pg/ml) in serum could be utilized.

7. Conclusion

As a conclusion, the study of the influence of serum inflammatory biomarkers in children found that the serum levels of YKL-40 were increased in those with Obstructive Sleep Apnea Syndrome (OSAS). YKL-40 levels were directly correlated with OAHI and LoSpO2,and the serum IL-8 levels were correlated specifically with OAHI. YKL-40 and IL-8 were significantly different between the mild and moderate-severe groups.YKL-40 together with IL-8 found to be specific serum inflammatory factors and which may provide an indication for the diagnosis and prediction of severity in children with OSAS. The cut-off value of serum levels of YKL-40 and IL-8 could be used as a reference value for clinical diagnosis. The limitation of invention and study might be the uneven distribution and severe OSAS were relativelyminor and therefore inflammatory markers in subgroups of OSAS need further optimization.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of the First Affiliated Hospital of Fujian Medical University. (IEC-FOM-013-1.0). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

In this manuscript, GC, YX and YW: designed the research, YW and YC: performed the research and the statistics, WL and MH: processed and interpreted of data, YW: wrote and revised the manuscript, GC: modified the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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.

Publisher's note

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Plasma tRF-16-79MP9PD and tRF-28-OB1690PQR304 as potential biomarkers for 4- to 7-year-old children with obstructive sleep apnea-hypopnea syndrome

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Background: We investigated the expression and the potential value of plasma transfer RNA-derived fragments (tRFs) of children with obstructive sleep apnea–hypopnea syndrome (OSAHS) as screening biomarkers.
Methods: At first, we randomly selected five plasma samples from the case group and the control group for high-throughput RNA sequencing. Secondly, we screened two tRFs with different expression between the two groups, amplified it by quantitative reverse transcription-PCR (qRT-PCR) on all samples. Then we analyzed the diagnostic value of the tRFs and their correlation with the clinical data.
Results: A total of 50 OSAHS children and 38 healthy controls were included. Our results demonstrated that the plasma levels of tRF-16-79MP9PD and tRF-28-OB1690PQR304 were significantly down-regulated in OSAHS children. Receiver operating characteristic curve (ROC) showed that the area under the curve (AUC) of tRF-16-79MP9PD and tRF-28-OB1690PQR304 was 0.7945 and 0.8276. In addition, the AUC of the combination reached 0.8303 with 73.46% and 76.42% sensitivity and specificity. Correlation analysis showed that the degree of tonsil enlargement, hemoglobin (Hb) and triglyceride (TG). were related to the expression levels of tRF-16-79MP9PD and tRF-28-OB1690PQR304. Multivariable linear regression analysis showed that degree of tonsil enlargement, Hb and TG related to tRF-16-79MP9PD while degree of tonsil enlargement and Hb related to tRF-28-OB1690PQR304.
Conclusions: The expression levels of tRF-16-79MP9PD and tRF-28-OB1690PQR304 in the plasma of OSAHS children decreased significantly which were closely related to the degree of tonsil enlargement, Hb and TG, may become novel biomarkers for the diagnosis of pediatric OSAHS.

KEYWORDS

obstructive sleep apnea-hypopnea syndrome, tRNA-derived fragments, biomarker, pediatrics, diagnostic screening

Abbreviations
tRNAs, transfer RNAs; tRFs, transfer RNA related fragments; tsRNAs, tRNA-derived small RNAs; OSAHS, obstructive sleep apnea–hypopnea syndrome; qRT-PCR, quantitative reverse transcription- Polymerase Chain Reaction; BMI, Body mass index; OAHI, Obstructive apnea hypopnea index; ROC, Receiver operating characteristic curve; AUC, area under the curve; HB, hemoglobin; TG, triglyceride; $LaSO_2$, lowest oxygen saturation; SBP, systolic blood pressure; DBP, diastolic blood pressure; Hb, hemoglobin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK-MB, creatine kinase-MB; UA, uric acid; BUN, blood urea nitrogen; TG, triglyceride; TC, total cholesterol.

1. Background

Obstructive sleep apnea-hypopnea syndrome (OSAHS) is a common disorder characterized by the snore and repeated episodes of partial or complete collapse of the upper respiratory tract during sleep (1). It has been widely accepted that hypoxia stress caused by upper airway obstruction in OSAHS can lead to systemic multiple system and organ damage (2). The main cause of upper airway obstruction in children is adenoid and/or tonsil hypertrophy (3). OSAHS can occur at all ages, with the peak of incidence occurring between 2 and 8 years old, and the most obvious clinical symptoms and surgical intervention mainly occur between 4 and 7 years old because of tonsil and adenoid hypertrophy accounting for the largest proportion of upper airway volume at this age (4, 5). The incidence of pediatric OSAHS is up to 1%–3% and is on the rise (6). OSAHS may lead to a series of pathological changes such as abnormal behavior, cognitive dysfunction, growth retardation and so on (7–10). In addition, many studies have shown that long-term OSAHS condition can increase the risk of diabetes, hypertension, metabolic diseases and cardiovascular diseases (11–13).

Transfer RNAs (tRNAs) are a class of non-coding RNAs that transport amino acids and assist protein synthesis (14). Under special conditions such as hypoxia, hunger and stress, pre- and mature tRNAs may generate new specific small RNA fragments after enzymatic splicing and chemical modification, which is called tRNA-derived small RNAs (tsRNAs) (15, 16). tsRNAs can also be mainly divided into tRNA halves and tRNA-derived fragments (tRFs) according to the cleavage loci and length (15). It has been reported that tRFs has a variety of biological functions, such as regulating translation level, affecting gene expression and inhibiting cell apoptosis (17). Recently, with the development of high-throughput sequencing and chip technology, novel tRFs have been gradually discovered and attracted researchers' interests. The relationship between tRFs and the occurrence of human diseases such as cancer and metabolic diseases has also been gradually revealed (18, 19).

Intermittent hypoxia is one of the typical characteristics of OSAHS, which can increase the expression of reactive oxygen species, resulting in systemic inflammation state, endothelial dysfunction and metabolic dysregulation (20). Therefore, biomarkers of hypoxia and oxidative stress may also be used to evaluate OSAHS. tsRNAs will be produced when cells are cleaved at specific tRNA sites in response to environmental stresses such as hypoxia, oxidative stress or viral infection (21). In recent years, several OSAHS-related differential microRNAs have been identified to be involved in a variety of pathophysiological processes (22, 23). Taken together, we speculate that tsRNAs may be related to the occurrence and development of OSAHS. In this study, we aim to explore the expression and the potential diagnostic screening value of plasma tRFs in children with OSAHS and further determine the association between tRFs and clinically relevant data in OSAHS children.

2. Methods

2.1. Research subjects

This study was an observational clinical study. We collected data from 50 patients aged 4–7 years old who were diagnosed with OSAHS after PSG based on medical history in Ningbo Women and Children's Hospital (Zhejiang, China) from November 2020 to December 2021. The diagnostic criteria of OSAHS refer to Chinese Guideline for the Diagnosis and Treatment of Childhood Obstructive Sleep Apnea (2020) (3), which diagnoses children with obstructive sleep apnea hypopnea index (OAHI) ≥1 events/h as OSAHS. Exclusion criteria for this study were children with congenital abnormalities of the nasolaryngology or airway, craniofacial malformation, anemia, digestive tract malformation, and those who had used antibiotics or probiotics in the last 3 months. In addition, 38 healthy control children were recruited as the control group and underwent free PSG examination.

In this study, basic information such as age, gender, body weight and height of all subjects were collected. Body mass index (BMI) was calculated by dividing weight by height squared.

This study has been approved by the ethical committee of Ningbo Women and Children's Hospital on November 5th, 2020 (Approval No. EC2020-047) and all participants have signed the informed written consent forms.

2.2. Specimen collection

All blood samples were collected from the peripheral venous blood of the children in Ningbo Women and Children's Hospital. For tsRNA studies, blood was firstly harvested into an ethylenediaminetetraacetic acid anticoagulation tube (EDTA). Within 1 h of blood collection, all specimens were centrifuged at 3,000 rpm/10 mins under 4°C to obtain plasma. The supernatant was transferred to RNase-free Eppendorf tubes and then stored at −80°C until RNA extraction.

2.3. tsRNA isolation and quality assessment

Total RNA, including tsRNA, was extracted and isolated from plasma samples by using TRIzol LS reagent (Invitrogen, Carlsbad, CA, USA) according to the instructions of manufacturer. RNA concentration was measured on NanoDrop™ Nd-1000 spectrophotometer (NanoDrop, Thermo Fisher Scientific, Inc., Wilmington, DE, USA) at 260 nm, 280 nm. The acceptance ratio standard for the study is 1.8–2.0. The extracted total RNA was stored at −80°C for subsequent experiments.

2.4. tsRNA pretreatment, small RNA library preparation and sequencing

In this study, plasma samples of 5 pairs of children with OSAHS and healthy controls were firstly selected. After

extracting total RNA, small isolated RNA was processed with the rtStarTM tRF and tiRNA Pretreatment Kit (Arraystar, Rockville, MD, USA) to remove the superfluous modification groups. Furthermore, compared to the original RNA, pretreated RNA had been purified twice to make it meet the concentration requirements for subsequent experiments. Purified RNA was then sent to Shanghai Kangcheng Company (Shanghai, China) for constructing small RNA libraries and performing small RNA sequencing analysis. Briefly, according to the requirements of the commercial kit NEB Next® Multiplex Small RNA Library Prep Set for Illumina (New England BioLabs, Inc., Ipswich, MA, USA), the pretreated RNA was bound with 3′ and 5′ adapters, and small RNA library was established after adding reverse transcription primers to synthesize cDNA. The Illumina NextSeq 500 (Illumina, Inc., San Diego, CA, USA) system was then used for sequencing.

In the original sequencing data, low-quality reads and short reads (<15 nt) should be firstly filtered. After this step, all selected RNA reads were aligned to several non-coding RNA database, such as miRBase database (http://www.mirbase.org/), Genomic tRNA database (http://gtrnadb.ucsc.edu/), tRFdb (http://genome.bioch.virginia.edu/trfdb/) and MintBase (https://cm.jefferson.edu/MINTbase/). In the expression of tsRNAs between OSAHS and healthy controls, the clean data was measured after the expression level was normalized. We believed that tsRNAs with a fold change of ≥2.0 and $P < 0.05$ are significantly different expressions. We chose tRF-16-79MP9PD and tRF-28-OB1690PQR304 for follow-up research.

2.5. Quantitative reverse transcription-polymerase chain reaction (qRT-PCR) verification of tsRNA sequencing results

Two thousand nanograms of RNA were reverse-transcribed to cDNA according to the instruction of the rtStar™ First-strand cDNA Synthesis Kit (Arraystar, Rockville, MD, USA). First step, input 1 μl of 3′ Adaptor, 0.5 μl of RNA Spike-in and nuclease-free water into 2000 ng RNA to make a total volume of 8.8 μl, then incubate the mixture at 70°C for 2 min. Second, we added 7.2 μl of 3′ Ligation Reaction Buffer, 1 μl 3′ Ligation Enzyme Mix and 1 μl of RNase Inhibitor in sequence, which was then incubated for 1 h at 25°C. Then the procedure involves addition of a 1 μl of nuclease-free water and 1 μl of RT-primer, and incubation for 5 min at 75°C, 15 min at 37°C, 15 min at 25°C. Third, 1 μl of 5′Adaptor (denatured), 2.5 μl of 10 mM ATP, 0.5 μl of 5′ Ligation Reaction Buffer, 1 μl of 5′ Ligation Enzyme Mix and 20 μl samples were mixed and incubated at 25°C at 1 h. Lastly, 25 μl of Adaptor-Ligated RNA, 8 μl of First-Strand synthesis reaction buffer, 3 μl of 0.1 MDTT, 2 μl of 2.5 mM dNTP Mix, 1 μl of RNase Inhibitor and 1 μl of Reverse Transcriptase were mixed in a nuclease-free tube, and the sample was heated for 60 min at 45°C, and then to 75°C for 15 min. qRT-PCR was firstly conducted on plasma samples of the previous 5 pairs of children with OSAHS and healthy controls, and the sequencing results of PCR products showed complete matching with tsRNA original sequence (**Figure 1**). After that, qRT-PCR was used to detect more differences in the expression levels of OSAHS children and healthy children, so as to verify whether it was consistent with the previous sequencing results. The qRT-PCR reaction was performed on a Mx3005P Real-Time PCR System (Stratagene, Palo Alto, CA, USA). The PCR primer synthesis (**Table 1**) and sequencing of PCR products were done by Sangon Biotech (Shanghai, China). U6 was used as an internal reference gene, and the relative gene expression was calculated as $\Delta CT = CT^{tRF} - CT^{U6}$, Larger ΔCT values indicate lower expression.

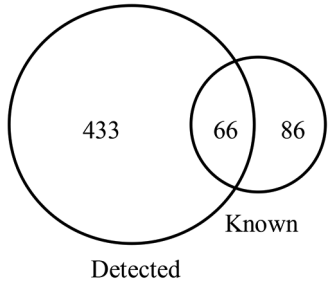

FIGURE 1
The number of tsRNAs detected in 5 OSAHS children and 5 healthy children plasma samples and the number of tsRNAs known in the tRFs database.

2.6. Statistical analysis

Statistical analysis was performed using SPSS version 24.0 and GraphPad Prism 8.0. The measurement data were expressed as mean ± standard deviation ($X \pm SD$) and the counting data were expressed in percentage (%). independent samples *t*-test was used to evaluate the significance of measurement data between the two groups. χ^2 test was used for comparison of counting data. Receiver operating characteristic (ROC) curve and area under the curve (AUC) were carried out to evaluate the diagnostic value of tRFs in OSAHS. Correlations between tRFs and relevant clinical parameters were analyzed by Pearson and Spearman correlation analysis. Multivariate linear regression analysis was performed to assess the association between plasma tRFs levels and several clinical parameters. All experiments were repeated at least three times independently. P value < 0.05 was considered statistically significant.

TABLE 1 Primer sequences involved.

Name	Sequence of primer
U6	F:5′ GCTTCGGCAGCACATATACTAAAAT 3′
	R:5′ CGCTTCACGAATTTGCGTGTCAT 3′
tRF-16-79MP9PD	F:5′ TACAGTCCGACGATCGTTTCC 3′
	R:5′GTGCTCTTCCGATCTGCTACACTA 3′
tRF-28-OB1690PQR304	F:5′ ACAGTCCGACGATCGAAAAAGT 3′
	R:5′ ATCTCCAACCCCATGGCCT 3′

3. Results

3.1. Participants' characteristics

A total of 50 OSAHS children and 38 healthy controls were enrolled. Parameters of all subjects are summarized in Table 2. There were significant differences in OAHI and lowest oxygen saturation ($LaSO_2$) between the OSAHS children and the controls. Besides, there were differences in height, serum creatinine (Scr) and total cholesterol (TC) between the two groups.

3.2. High-throughput sequencing results

Among the 10 sequencing libraries, the average number of original reads was about 6.69 million and the average reads ratio of high-quality bases was about 96.97%. Among them, microRNAs accounted for the highest proportion, with an average read number of 935,592.4 (17.64%). The average reads of mature tRNA and precursor tRNA were 156,419.3 (3.04%) and 5,973.1 (0.12%). A total of 499 tsRNAs were detected, of which 66 were recorded in the tRF database (Figure 1). Through the comparison between the two groups, there were 11 tsRNAs that were significantly differentially expressed, of which two tsRNAs were up-regulated and the remaining 9 tsRNAs were down-regulated (Figure 2). Taking into account the fold change, *P* value and tsRNAs expression difference between two groups, we selected tRF-16-79MP9PD and tRF-28-OB1690PQR304 as our research objects. After that, we designed primers for the two tsRNAs, and the sequencing results of the qRT-PCR products proved the specificity of the primers (Figure 3).

TABLE 2 All parameters of participants.

Groups	HC ($n = 38$)	OSAHS ($n = 50$)	t/χ^2	*P*-value
Age (years)	5.63 ± 0.75	5.35 ± 0.81	−1.667	0.0990
Male, *n* (%)	22 (58%)	27 (54%)	0.133	0.7160
Height (cm)	115.40 ± 9.38	111.90 ± 6.61	2.065	0.0420*
Weight (kg)	21.34 ± 4.15	20.78 ± 4.60	0.592	0.5557
BMI (kg/m^2)	15.93 ± 1.80	16.50 ± 2.47	1.201	0.2330
OAHI (events/h)	0.18 ± 0.13	8.94 ± 4.56	11.840	<0.0001****
$LaSO_2$ (%)	90.58 ± 3.42	70.68 ± 14.63	8.206	<0.0001****
SBP (mmHg)	101.60 ± 6.96	102.40 ± 10.76	0.373	0.7098
DBP (mmHg)	61.26 ± 7.57	63.78 ± 7.77	1.522	0.1316
Hb (g/dl)	12.72 ± 0.77	12.39 ± 0.99	1.661	0.1007
ALT (U/L)	11.87 ± 3.99	12.91 ± 6.20	0.904	0.3684
AST (U/L)	28.66 ± 5.58	30.60 ± 6.66	1.451	0.1504
CK-MB (U/L)	24.36 ± 8.59	25.43 ± 4.48	0.757	0.4514
UA (μmol/L)	277.40 ± 62.25	260.10 ± 55.99	1.373	0.1732
Scr (μmol/L)	45.82 ± 9.96	51.85 ± 7.32	3.276	0.0015**
BUN (mmol/L)	5.12 ± 1.35	4.96 ± 1.34	0.572	0.5690
TG (mmol/L)	1.01 ± 0.43	1.21 ± 0.59	1.690	0.0947
TC (mmol/L)	4.29 ± 0.59	4.60 ± 0.66	2.306	0.0235*
Glucose (mmol/L)	5.13 ± 0.91	5.14 ± 0.73	0.099	0.9218

HC, healthy control; BMI, body mass index; OAHI, obstructive apnea hypopnea index; $LaSO_2$, lowest oxygen saturation; SBP, systolic blood pressure; DBP, diastolic blood pressure; Hb, hemoglobin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK-MB, creatine kinase-MB; UA, uric acid; BUN, blood urea nitrogen; TG, triglyceride; TC, total cholesterol.
*$p < 0.05$, ** $p < 0.01$, **** $p < 0.0001$.

3.3. Expression levels of tRF-16-79mp9pd and tRF-28-OB1690PQR304

To further investigate the differential expression of tRF-16-79MP9PD and tRF-28-OB1690PQR304 in OSAHS children, we verified the expression of both tRFs in an extended cohort. As expected, our results showed that the expression levels of tRF-16-79MP9PD and tRF-28-OB1690PQR304 were significantly lower in patients with OSAHS than in controls (both, $P < 0.0001$), which was consistent with the results of high-throughput sequencing (Figure 4).

3.4. Potential diagnostic values of tRF-16-79mp9pd and tRF-28-OB1690PQR304

The ROC analysis revealed that the AUCs of tRF-16-79MP9PD and tRF-28-OB1690PQR304 were 0.7945 with 52% sensitivity and 94.74% specificity (Figure 5A), 0.8276 with 79.59% sensitivity and 71.05% specificity, respectively (Figure 5B). Furthermore, the AUC of the combination reached 0.8303 with 73.46% sensitivity and 76.32% specificity (Figure 5C).

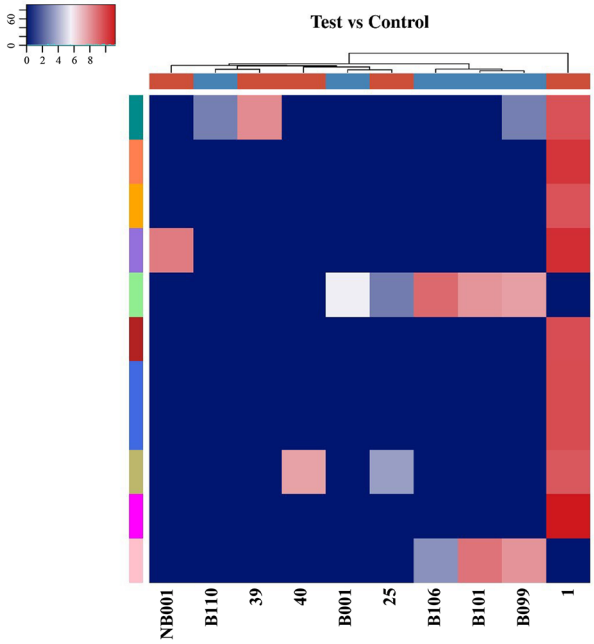

FIGURE 2
The difference of tsRNAs expression between OSAHS children and healthy children was analyzed by hierarchical clustering heat maps. Each row represented a tsRNA and each column represented a sample. The 25, 1, 39, NB001, and 40 were plasma specimens of children with OSAHS. The B009, B110, B106, B001, and B101 were plasma specimens of normal children. The degree of difference gradually increases from blue to red.

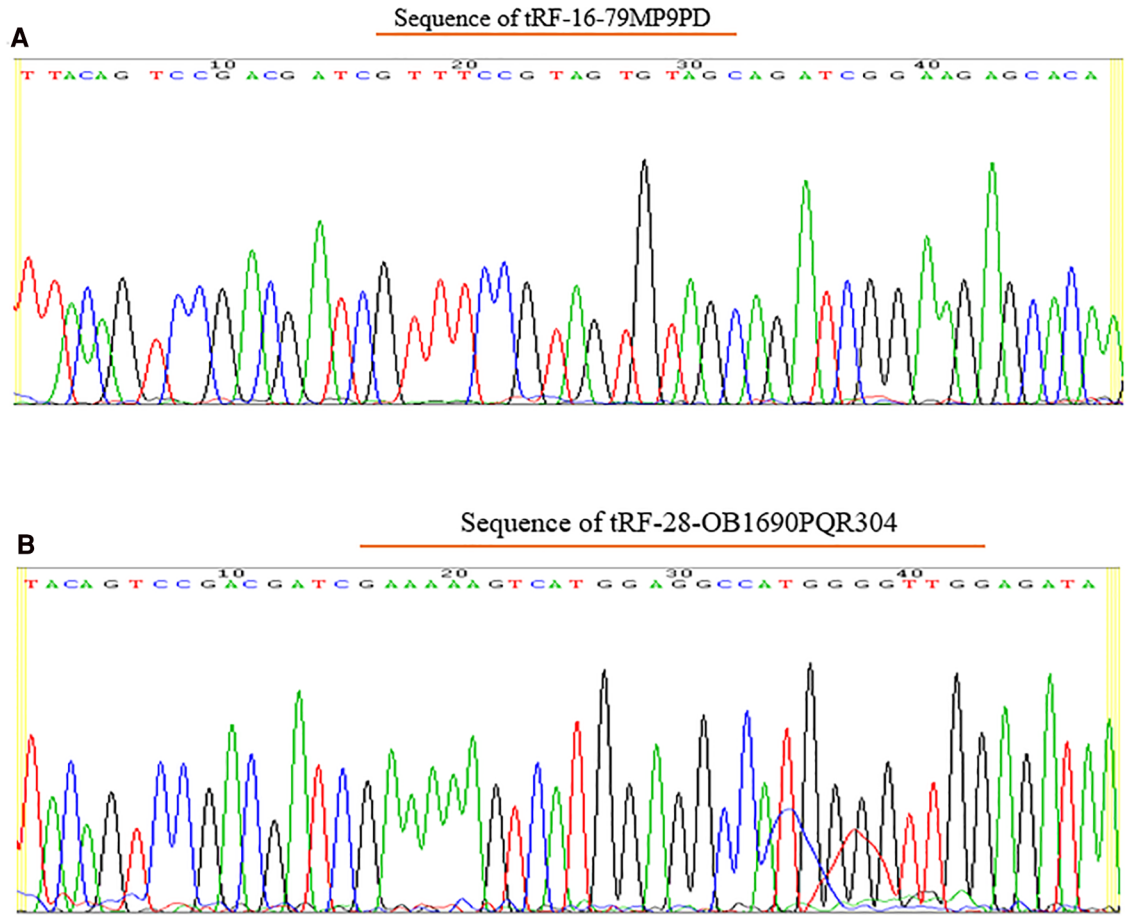

FIGURE 3
Sequencing results of qRT-PCR products of tRF-16-79MP9PD (A) and tRF-28-OB1690PQR304 (B).

3.5. Correlations between tRFs and clinical parameters

Firstly, we used simple linear correlation to analyze the correlation between tRF-16-79MP9PD and tRF-28-OB1690PQR304 and the clinical parameters we collected. The visual correlation heat map (Figure 6) showed the correlation between all parameters. We found that the level of tRF-16-79MP9PD was significantly correlated with the degree of tonsil enlargement, Hb, TG and CK-MB level (Figures 7A–D) while tRF-16-79MP9PD was correlated with the degree of tonsil enlargement, Hb and TG (Figures 7E–G).

Subsequently, we performed multiple linear regression using the regression method. The results showed that degree of tonsil enlargement, Hb and TG levels were related to the tRF-16-79MP9PD expression (Table 3) whose mathematic model was $y = -10.309 + 0.902x_1 + 1.887x_2 - 0.160x_3 + 1.656x_4$. Differently, Hb and the degree of tonsil enlargement were related to tRF-28-OB1690PQR304 (Table 4) whose mathematic model was $y = -14.383 + 1.353x_1 + 2.503x_2$.

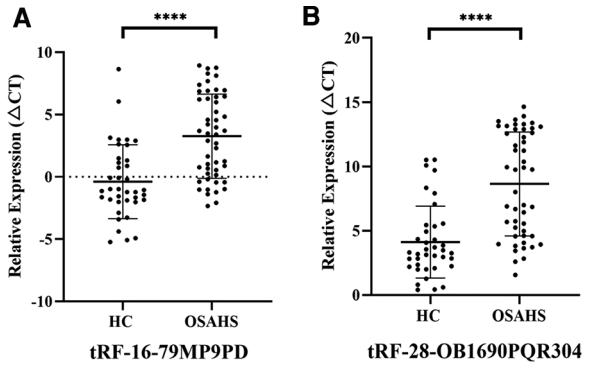

FIGURE 4
Expression of tRF-16-79MP9PD (A) (t = 5.289, 95% CI: 2.278–5.022) and tRF-28-OB1690PQR304 (B) (t = 5.886, 95% CI: 2.994–6.049) in patients with OSAHS. ****$p < 0.0001$; CI, Confidence Interval.

4. Discussion

As one of the most serious diseases among childhood sleep disordered breathing, OSAHS is characterized by hypoventilation, decreased blood oxygen saturation and disrupted sleep structure (24). Currently, guidelines recommend PSG as a standard diagnostic method for pediatric OSAHS. However, standard PSG

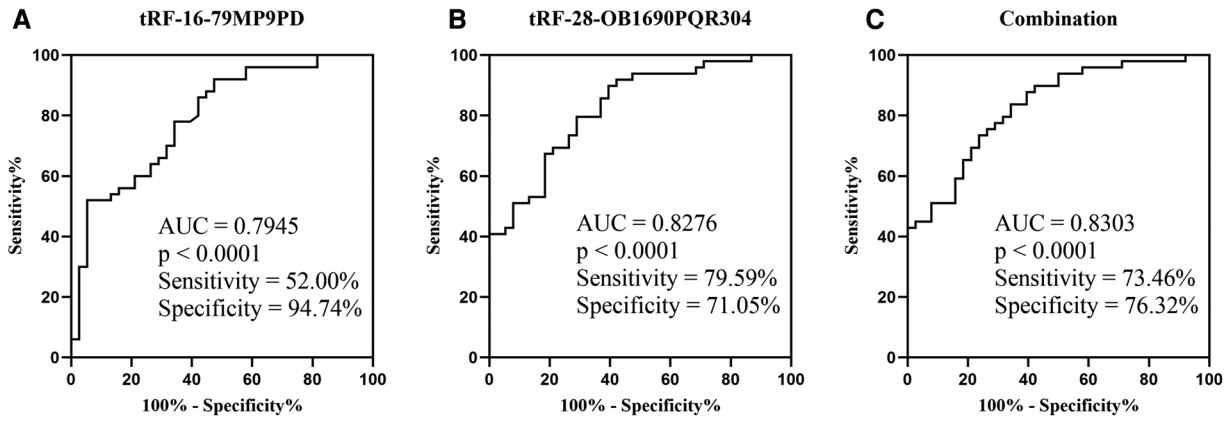

FIGURE 5
ROC of plasma tRF-16-79MP9PD (A) (SE: 0.0478, 95% CI: 0.7007–0.8882), tRF-28-OB1690PQR304 (B) (SE: 0.0433, 95% CI: 0.7428–0.9124) and the combination (C) (SE: 0.0428, 95% CI: 0.7465–0.9141; OR: tRF-16-79MP9PD: 1.1219, tRF-28-OB1690PQR304: 0.6419). SE, Standard Error; OR, Odds Ratio.

monitoring is limited by the equipment, operation, personnel and cost of standard PSG monitoring. Although many efforts have been made to explore biomarkers of OSAHS, there is currently no definite biomarker available in the clinic.

tsRNAs exist widely in tissues and cells of various organisms with tissue specificity and disease correlation and can play roles in cell proliferation, regulation of gene expression, RNA processing, modulation of DNA damage response and tumor suppression (25). tRFs can be expressed and measured in human body fluids such as serum, plasma and urine. In addition, they are not easily to be degraded by RNase due to their short length. Thus, tRFs have great potential to serve as a non-invasive biomarker for various diseases (18). Accumulating evidence has demonstrated tRFs serve as ideal biomarkers and therapeutic targets in a variety of diseases, such as

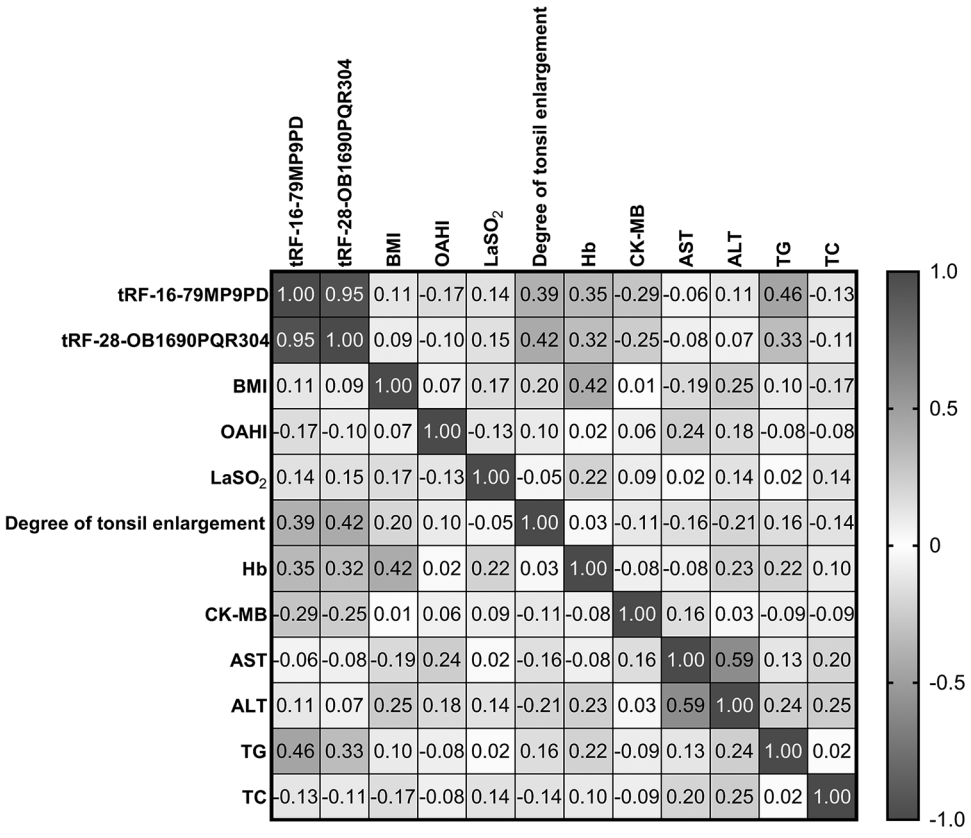

FIGURE 6
The visual correlation heat map of correlation between tRF-16-79MP9PD and tRF-28-OB1690PQR304 and the clinical parameters.

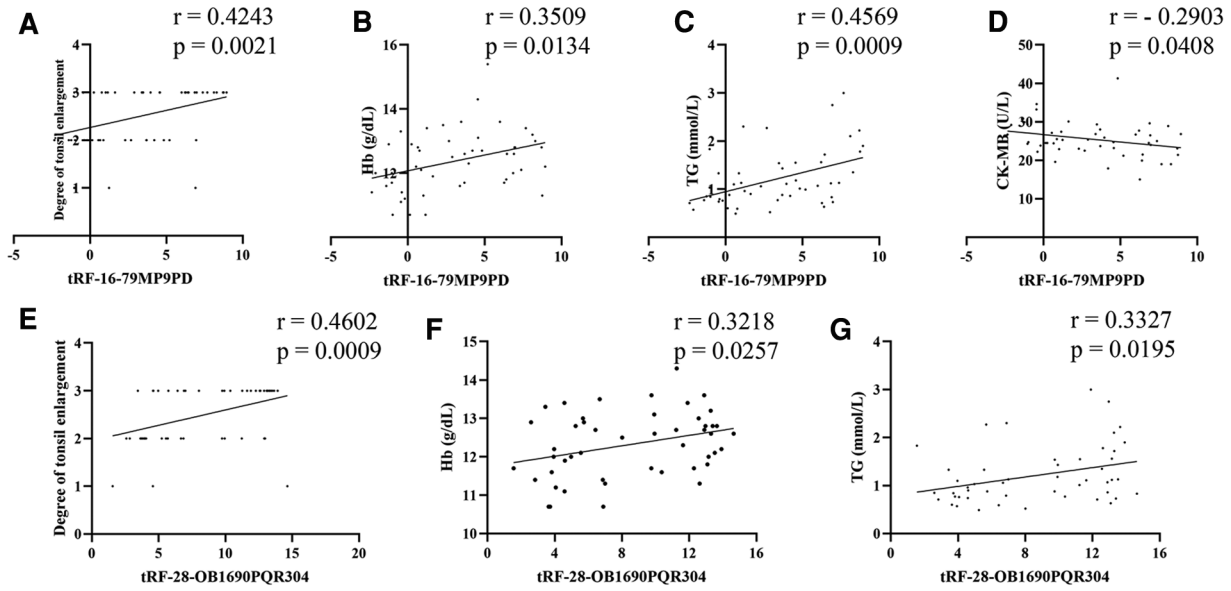

FIGURE 7
Correlation between tRF-16-79MP9PD and the degree of tonsil enlargement (A), Hb (B), TG (C) and CK-MB (D) level, tRF-28-OB1690PQR304 and the degree of tonsil enlargement (E), Hb (F), TG (G). Hb, hemoglobin, TG, triglyceride, CK-MB, creatine kinase-MB.

prostate cancer (26), pancreatic ductal adenocarcinoma (27) and systemic lupus erythematosus (28).

To our knowledge, this study was the first to investigate the plasma tRFs levels in children with OSAHS. Specifically, we first analyzed general baseline data of the OSAHS and HC groups. The results showed that the height of children with OSAHS was lower than that of HC group, which was consistent with the research of Johnson C (29) and may due to the decrease of growth hormone secretion caused by poor sleep quality of children with OSAHS. Similarly, the two groups had statistical differences in Scr and TC, which was consistent with the studies of other scholars (30, 31). Secondly, we performed small RNA sequencing to detect the expression profile of tRFs in 5 pairs of OSAHS children and control specimens. The results showed that the expression of 11 tsRNAs was significantly different between the two groups. Two dysregulated tRFs: tRF-16-79MP9PD and tRF-28-OB1690PQR304 were screened out based on fold changes, *P* value and tsRNAs expression differences. Subsequently, qRT-PCR was performed in the extended cohort to verify the authenticity of the sequencing results. It was proved that the expression levels of tRF-16-79MP9PD and tRF-28-OB1690PQR304 were down-regulated in the OSAHS group compared with the HC group, which was consistent with the results of small RNA sequencing, indicating that the decreased expression of tRF-16-79MP9PD and tRF-28-OB1690PQR304 were closely related to OSAHS.

In addition, we further evaluated the diagnostic efficacy of tRF-16-79MP9PD and tRF-28-OB1690PQR304 by ROC curve analysis, and the results demonstrated that tRF-16-79MP9PD and tRF-28-OB1690PQR304 had high sensitivity and specificity to distinguish OSAHS from healthy children, processing AUCs of 0.7945 with 52% sensitivity and 94.74% specificity, 0.8276 with 79.59% sensitivity and 71.05% specificity, respectively. More importantly, the AUC of their combination increased to 0.8303 with 73.46% sensitivity and 76.32% specificity, suggesting the great potential of tRF-16-79MP9PD and tRF-28-OB1690PQR304 as diagnosis biomarkers for childhood OSAHS. At present, studies on OSAHS in children have not obtained clear biomarkers, and existing studies also have some limitations, such as lack of specificity and sensitivity analysis (32). In our study, the AUC of the joint diagnosis of two tRFs exceeds 0.83, and the sensitivity and specificity exceed 70%, which has certain clinical screening diagnostic value. As a clinical OSAHS screening indicator, tRF can serve as a new research direction, but its

TABLE 3 Multivariate linear regression analysis of plasma tRF-16-79MP9PD level and clinical parameters.

Associated parameters	B	SE	95% CI	*t*	*P*-value
Hb (x_1)	0.902	0.421	(0.053, 1.752)	2.141	0.038
TG (x_2)	1.887	0.684	(0.509, 3.266)	2.759	0.008
CK-MB (x_3)	−0.160	0.087	(−0.336, 0.016)	−1.828	0.074
Degree of tonsil enlargement (x_4)	1.656	0.643	(0.360, 2.953)	2.575	0.013
Constant	−10.309	5.999	(−22.400, 1.782)	−1.718	0.093

TABLE 4 Multivariate linear regression analysis of plasma tRF-28-OB1690PQR304 level and clinical parameters.

Associated parameters	B	SE	95% CI	*t*	*P*-value
Hb (x_1)	1.353	0.615	0.114, 2.592	2.199	0.033
Degree of tonsil enlargement (x_2)	2.503	0.845	0.802, 4.204	2.963	0.005
Constant	−14.383	7.690	−29.871, 1.104	−1.870	0.068

diagnostic value needs to be evaluated in multi-center studies with larger sample sizes.

Furthermore, we analyzed the correlation between tRFs levels and laboratory parameters in OSAHS children. We found that the expression levels of tRF-16-79MP9PD and tRF-28-OB1690PQR304 were closely related to the degree of tonsil enlargement. At the same time, we found that the expression level of tRF-16-79MP9PD was also significantly correlated with Hb, TG and CK-MB level. Multivariable linear regression analysis showed that Hb, TG and degree of tonsil enlargement were related to tRF-16-79MP9PD. In addition, tRF-28-OB1690PQR304 was significantly correlated with Hb and TG. The degree of tonsil enlargement and Hb were related to the tRF-28-OB1690PQR304 level through multivariable linear regression analysis. Thus, the plasma levels of tRF-16-79MP9PD and tRF-28-OB1690PQR304 are related to a variety of laboratory indicators in OSHAS. More experiments are needed to investigate the role of tRF-16-79MP9PD and tRF-28-OB1690PQR304 in OSAHS.

Nevertheless, there are still some limitations to our study. Firstly, the sample size of this study was 50 OSAHS children and 38 healthy controls. Further expansion of sample size is needed to evaluate the diagnostic value of tRFs. Secondly, this study did not explore the function of tRFs by combining the pathological and physiological mechanisms of OSAHS. In the future, we will explore the role of tRFs in the pathogenesis of OSAHS based on this research. Thirdly, this study was limited to children in Ningbo City. Considering regional and racial differences, future multicenter and larger sample size studies are needed to evaluate the value of tRF as a biomarker.

5. Conclusions

In conclusion, our study identified that the plasma levels of tRF-16-79MP9PD and tRF-28-OB1690PQR304 were down-regulated in 4- to 7-year-old children with OSAHS and were closely related to the clinical parameters of OSAHS children. tRF-16-79MP9PD and tRF-28-OB1690PQR304 may be used as a new potential biomarker for the diagnosis of pediatric OSAHS.

Data availability statement

The data presented in the study are deposited in the NCBI BioProject repository, accession number PRJNA862251.

Ethics statement

The studies involving human participants were reviewed and approved by medical Ethics Committee of Ningbo Women and Children's Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

JW and ZS conceived and designed the study, and reviewed and revised the manuscript. XC and YL analyzed and drafted the initial manuscript. YS completed the PCR experiment in this study and wrote the method of manuscript. QL coordinated and supervised data analyses, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. JW and XC contributed equally to this work. ZS and QL contributed equally to this work. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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.

Publisher's note

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150th Anniversary of global adenoid investigations: unanswered questions and unsolved problems

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Although the problem of adenoid hypertrophy (AH) has been diagnosed and treated by doctors and scientists from around the world for the last 150 years, there is still no consensus regarding appropriate diagnosis, conservative treatment options, and qualification for surgery. This manuscript presents current knowledge on these issues and compares diagnostic methods and the effectiveness of treatment options. Factors that may influence the obtained treatment results are also described, and a questionnaire is proposed to compare the results of treatment. The objective of drawing attention to this problem is to obtain better results from conservative treatment in the future and better-qualified patients for surgical treatment.

KEYWORDS

adenoid hypertrophy, adenoid hypertrophy treatment, conservative treatment, AH, adenoid surgery

Introduction

Although the pharyngeal tonsil was first discovered and described by Conrad Victor Schneider in 1,661 as a prominent nasopharynx structure, it was only 150 years ago, in 1873, that the medical world started to concentrate its attention on this important field of children's disease (1, 2). Such interest was motivated by Hans Wilhelm Meyer's second publication, "Ueber adenoide Vegetationen in der Nasenrachenhohle," in Arch. f. Ohrenheilkunde 1873, T-11 Bd. S. 211. VIII B., S. 120 and 241. Meyer is the father of the term "adenoid" and published the first report on an adenoid surgical resection in 1868 (**Figure 1**). However, although this first scientific report was significant, it attracted little attention. What would be the breakthrough manuscript was published by Wilhelm Meyer five years later, when he described his observations and experience in the surgical treatment of adenoids (2). From that time on, the medical world started paying more attention to this important field of disease. Specifically, the role and function of this nasopharyngeal structure in the pathogenesis of recurrent upper respiratory tract infection and rhinorrhoea began to be investigated by doctors. Adenoid hypertrophy (AH) was also found to be related to otitis media with effusion (3). Moreover, the concept of a "united airway disease" suggested that AH and rhinitis may have impact on the lower respiratory tract, which was confirmed in children suffering from asthma (4).

AH is one of the most common disorders in children. All associated indications, such as mouth breathing, snoring, nasal blockage, chronic rhinitis, and nasal speech are called "adenoid symptoms". The consequent obstruction of the nose may also cause recurrent

FIGURE 1
Hans Wilhelm Meyer.

sinusitis, asthma, sleep apnoea, and otitis media with effusion. In some cases, AH may cause serious health deterioration and impair child development (5). For instance, Bitar et al. showed that 57.7% of young children suffering from nasal blockage and admitted to ENT outpatient clinics had AH (6).

Diagnosis

What is the best method for diagnosing adenoid hypertrophy?

The father of adenoid diagnostics, Hans Wilhelm Meyer, used his finger to explore the patient's mouth to confirm hypertrophy. He described his own methods of diagnosis in 1868 and was the first to perform resection surgery with an adenotome (7). Since then, many diagnostic methods have been introduced in the search for the most accurate approach, as well as the one that is most comfortable and least burdensome for patients, most of whom are young, not well cooperative children. Invasive techniques and imaging technology were later implemented. For the first group of diagnostic techniques, physical examinations were performed through the mouth or nose. For many years, doctors would palpate the adenoids with a finger then use the less traumatic approach of transoral mirror examination. The development of rigid and later flexible nasopharyngoscopies allowed for a pharyngeal examination to be performed through the nose. Thinner rigid nasopharyngeal endoscopy (RNE) and flexible nasopharyngeal endoscopy (FNE) became common methods for nasopharyngeal examination. Additionally, video fluoroscopy and acoustic rynomanometry for nasal diagnosis were developed. The second diagnostic tool group consisted of lateral x-ray of the nasopharynx (lateral cephalogram), ultrasonography, computer tomography (CT), and magnetic resonance imaging (MRI) (8–12).

The results of these initial tests were often based on the doctors' own experiences of feeling what is often immeasurable. Other results are based on measurable parameters, which do not always have to be related only to AH. In some cases, the condition may be simulated by other reasons (i.e., thermal seasons). Other factors related to nose and nasopharyngeal obstruction include nasal concha hypertrophy, nasal septal deviation, polyps, and allergic rhinitis (9, 13). The presence of such conditions can make it difficult to objectify and compare the results. Newly introduced diagnostic methods should still be compared to the results of transoral mirror examination or nasal endoscopy to ensure effectiveness (9, 12–14). However, this only occurs in some cases. Furthermore, in selected cases, the results of the intraoperative mirror exam may not correlate with preoperative FNE. Such circumstances may arise in children with small- and medium-sized adenoid hypertrophy (A/C ratio beneath 75%) (9). Moreover, Patel suggests that intraoperative mirror examination performed in a horizontal position in anaesthesia with relaxation may also be fraught with observation errors (9).

The sensitivity and specificity of lateral x-rays of the nasopharynx (lateral cephalometry) have reached 61%–75% and 41%–96% respectively (10, 15). More objective results are achieved when the diagnostician takes an x-ray picture at the end of patient's inspiration phase. This is especially difficult in the case of young, non-cooperating, and often frightened children (16). According to Major et al., the size of the adenoid is often overestimated in lateral cephalometry. As a result, lateral x-rays are useful for measuring the free airway space between the adenoid and soft palate (15). This is due to the fact that the diagnostic results of lateral cephalometry are shown in a single two-dimensional summation picture (15–17). As an alternative, lateral cephalometric radiographs are a simple, non-expensive, sufficiently informative method. Moreover, new digital x-ray apparatuses decrease radiation expousure (15, 17). While Mlynarek at al. did not find a correlation between lateral cephalometry and obstructive symptoms scores (OSS), a relationship has been identified between FNE and OSS (18). However, in another study, Caylakli found a correlation between the results of lateral cephalometry and those of FNE (19).

The high radiation doses of other available imaging methods, such as computer tomography (CT), cone bean computer tomography (CBCT), and time consuming such as magnetic resonance imaging (MRI) exclude these methods from being used repeatedly (20). From that reasons promising seems to be ultrasonography of the adenoid tissue. Wang et al. tried to assess

AH with ultrasonography, and despite the encouraging results, further evaluation is needed (21).

A definite advantage of invasive diagnostics, in addition to the static assessment of anatomical structures, is their ability to obtain dynamic information on the functioning of the nose and nasopharynx. In these examinations, a colour image is obtained, which allows for differentiation between the physiological and inflammatory conditions of the mucous membrane, as characterised by the type of mucous in the nose and its coverage of the adenoids.

Invasive nasopharyngeal diagnostics may cause discomfort and pain. In the absence of the child's cooperation, general anaesthesia is required, but such circumstances are rare for an experienced paediatric laryngologist. According to Ysunza et al., video fluoroscopy of the nasopharynx shows high sensitivity (100%) and specificity (90%). Unfortunately, this diagnostic tool produces a 260 micro-sievert irradiation dose (10, 15). Flexible nasopharyngoscopy is less traumatic than rigid endoscopy, and mentioned above, it may be performed without anaesthesia and provide important information about the nose, nasopharynx, and adenoid state (22, 23). In the context of COVID-19 tests, in the patients' opinions, this examination is less painful than testing with a COVID-19 nasal-swab. The sensitivity and specificity of flexible nasopharyngoscopy in the assessment of AH have reached 97.3% and 72.7%, respectivly (24). Today, flexible endoscopic examination should be the gold standard in AH examination and serve as a reference test for newly introduced diagnostic methods.

What should be appreciated for adenoid hypertrophy classification?

In clinical adenoid evaluation in children, the percentage of nasopharyngeal space occupied by the adenoid is most often used for adenoid size assessment. This is referred to as the adenoid-to-choana scale or ratio (A/C scale, A/C ratio) and is usually measured with an accuracy of up to 5%. For better assessment of patient groups, different anatomical and clinical classifications are used. In fact, many authors have introduced their own AH classifications. Although they are often similar, each may contain its own modified concept of the anatomical assessment of nasopharyngeal structures in relation to a particular clinical condition. The most common classification has been proposed by Cassano and is based on a four-step pictorial scheme describing the occupation of the nasopharynx by the adenoid (I° - 0%–25%, II° - 26%–50%, III° - 51%–75%, or IV° - 76%–100%) (25). In another five-step scale introduced by Zalzal, 0° indicates 0% obstruction of the choanae,1° less than 40% obstruction, 2° 41%–70% obstruction, 3° 71%–90% obstruction, and 4° complete obstruction (91%–100%), with adenoid tissue touching the relaxed soft palate (26). Another three-degree classification of AH was proposed by Parikh and Bolesławska (27, 28). Some of these classifications also differentiate relations between the adenoid and eustachian tube (27, 29). Flexible endoscopic adenoid investigation also allows for the classification of mucous coverage of the adenoid. For these reasons, the Mucus of Adenoid Scale by Nasopharyngoscopy Assessment (MASNA) was proposed. This four-point classification scheme accounts for the amount of mucus covering the adenoid (0° corresponds to no mucus, 1° describes the residue of clear watery mucus, 2° indicates some amount of dense mucus, and 3° indicates copious, thick, dense mucus; **Figure 2**) (23). In light of many proposed and used scales, there is still an important question that remains: what degree of AH is indicative of a large adenoid which should be surgically removed? This would help unify the results and facilitate further analysis.

What does it mean for an adenoid to be large?

In our daily practice, we often encounter patients who have previously been examined by other doctors who, based on anterior rhinoscopy and symptoms reported by parents, declare that the adenoid is large and suggest its removal. Unfortunately, these statements often do not correlate with endoscopic examination of the nasopharynx. Our intraoperative comparison of adenoid size with preoperative endoscopic adenoid assessment indicated that a 75% A/C ratio or more is equivalent to an intraoperatively removed large adenoid (24). For this reason, the classification proposed by Cassano seems to be more adequate for AH assessment because the degree of AH in this scale is equal to a large adenoid, and, in this case, adenoidectomy should be considered (25).

Does the adenoid involute with age? Is it worth waiting for an adenoidectomy?

For the most part, knowledge about adenoid tissue involution is based on Scammons's theory, which is over 100 years old, and ENT doctors' own experiences in treating children (30). According to Scammon's curves, adenoid tissue grows during childhood, leading to involution in adulthood (30). Still, there is a general lack of longitudinal observational studies on adenoid development in children, and only three are based on lateral nasopharynx x-rays studies. As shown above, lateral cephalometry may overestimate adenoid size and should be used specifically for measuring the narrowest airway space between the nose and the nasopharynx (15, 17, 31, 32). Our study showed that the involution of the adenoid proceeds slowly (24). Endoscopic examinations in the analysed group of preschool children indicated that in only 7.9% of the children, adenoid size changed by more than 15% on the A/C scale after one year of observation. In 21.6% of children, this change occurred over a period of two years, and over a period of three years in 45%.

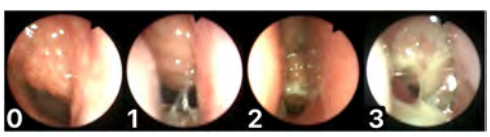

FIGURE 2
Mucus of adenoid scale by nasopharyngoscopy assessment (MASNA), 0—no mucus, 1—residue of clear watery mucus, 2—some amount of dense mucus, 3—copious thick dense mucus.

These findings are similar to the results of the longitudinal lateral cephalometric studies performed by Yamada, which showed that an overgrowth of adenoids appeared in preschool children, but there were no significant changes in the adenoid size at 8–12 years age (32). The growth and development patterns of nasopharynx lymphoid tissues are different for each patient. In our opinion, there is still a need for an accurate and broad analysis of adenoid involution in children with the use of objective adenoid size assessment.

Treatment

What is an adequate conservative medical treatment for adenoid hypertrophy?

Various methods of conservative treatment of AH have been used thus far. Their results are often difficult to evaluate because many studies have not undertaken a classic assessment of the size of the adenoid or its mucus coverage, instead only analysing the reduction of ailments and adenoid symptoms or, for example, performing a spirometry test. Therefore, the maximal conservative medical treatment of AH and how long it should last is still not known.

Intranasal topical steroids

Intranasal steroid treatment has been the most common treatment for AH and related symptoms for many years. Numerous studies have confirmed the beneficial effect of topical steroids on complaints related to AH or for decreases in adenoid symptoms (**Table 1**) (33–46). Significantly less publications refer to the objective postoperative assessment of adenoid size. According to Jazi at al., adenoid tissue regression after steroid treatment in FNE examination was less significant than what would be considered clinical improvement (44). However, *in vitro* clinical trials showed some impact of corticosteroids on reducing adenoid tissue proliferation (47). These effects were confirmed by the identification of the GCR-α and GCR-β human glucocorticoid receptors in adenoid tissue (48). These two receptors are ligands for glucocorticoid and regulate the tissue response for steroids (48). It should be emphasized that there is

TABLE 1 Research on the effect of topical steroids on adenoid size or symptoms.

Author/ year/ country	Age	Number of patients treated with steroids	Medication	Time of treatment	Time of final results counting	Main results
Cengel (33) 2005 Turkey	3–15	122	MF	6 weeks	at the end of therapy	improvement of OME in 42.2% of children
Ciprandi (34) 2007 Italy	3–6	139	F	8 weeks	at the end of therapy	reduction of A/C ratio in 72% patients
Demirhan (35) 2010 Turkey	4–16	25	MF	8 weeks	at the end of therapy	symptoms improvement, adenoidectomy was not necessary in 76% of children
Mohebi (36) 2014 Iran	2–11 (2–4 and 5–11)	51	MF	3 months	at the end of therapy	improvement
Gupta (37) 2015 India	4–12	55	MF	4 weeks	at the end of therapy	improvement
Monga (38) 2020 India	3–11	30	MF	8 weeks	at the end of therapy	improvement
Rezende (39) 2015 Brazil	4–8	55	MF	6 weeks	at the end of therapy	decrease of adenoid size
Hassanzadeh (40) 2016 Iran	4–12	20	MF	4 weeks	at the end of therapy	decrease of adenoid size
Lepcha (41) 2002 India	3–12	13	B	8 weeks	at the end of therapy	**no improvement**
Berlucchi (42) 2008 Italy	3–7	21	MF	1–3 months before surgery or 15–31 months (mean 23) (2 weeks every month, suspended during the summer)	Before surgery (9 children) or at the end of the maintenance therapy (12 children)	Long-time MF therapy may obtain successful results
Criscuoli (43) 2003 Italy	Mean 3,8	53	B	26 weeks	24,52,100 weeks after treatment	relevant clinical improvement in 45% children immediately after therapy, finally, after 2 years 70% children performed surgery
Jazi (44) 2011 Iran	2–10	20	MF	6 weeks	1 and 8 weeks after treatment	adenoid regression in FNE was less significant than clinical improvement
Bhargava (45) 2014 India	2–12	100	MF	24 weeks	24 weeks after treatment	clinical improvement
Zwierz (46) 2022 Poland	3–6	165	MF	3 months	3 to 6 months after end of the treatment	no long-time effect of intranasal mometasone furoate on adenoid size, its mucus

MF, mometasone fluroate; F, flunisolide; B, beclomethasone.

a lack of studies on the long-term outcomes of AH treatment with nasal steroids on adenoid size in children. Almost all the existing research has analysed changes of adenoid symptoms or measured adenoid size (A/C ratio) immediately after conservative treatment and not after a leeway period without the usage of topical steroids. The reports presented by Criscuoli are staggering, indicating that 70% children undergo adenoidectomy in the two-year follow-up period after treatment, despite the fact that immediately after treatment, 45% of children achieve significant improvement in their symptoms (43). Our long-term results 3–6 months after the discontinuation of medication did not indicate an adenoid size change and suggest that the therapy should be used continuously for a long-term period. A low rate of side effects allows for these steroids to be used topically for a long period of time (43, 46, 49, 50). This tendency is especially visible in recent works, where the period of use of nasal steroids has been extended (42, 43).

Antihistamine drug therapies

It is estimated that 20%–40% of children worldwide are affected by allergic rhinitis (AR) (51, 52). A study performed by Eren et al. showed that skin prick tests were positive in 65.2% of young patients with AH symptoms (53). The prevalence of AH has been increased in children with allergies, which means that this treatment could only be effective in this group of patients (54). However, there is a discrepancy in age predominance in children diagnosed with AH and AR. AH is diagnosed between 3 and 4 years of age, whereas AR is usually diagnosed in children 6–7 years old. Moreover, the remaining group of patients with nonallergic rhinitis was not homogenous. These cases included local allergic, drug-induced, gustatory, atrophic, occupational, hormonal, cold-air induced, and idiopathic rhinitis. It seems that in this nonallergic rhinitis group, the most common form is local allergic rhinitis (LAR). The incidence of LAR in children ranges from 3.7% to 66.6% (55). LAR seems to be an underdiagnosed entity and not considered for the doctors.

Both allergic and nonallergic rhinitis are cases of chronic rhinitis characterised by the presence of inflammatory cells that act on the nasal mucosa. Activation of the mast cells in nonallergic rhinitis cause histamine and a variety of other mediators (e.g., eosinophil chemotactic factor of anaphylaxis, PAF, leukotrienes, and prostaglandins) to release that exacerbate the inflammatory reaction (56). The release of histamine also acts chemotactically on neutrophils. Since a significant group of children with AH may be affected by both AR and LAR, local or systemic antihistamine treatment may be initiated in the case of strong symptoms, such as sneezing, rhinorrhoea, congestion, and nasal itching. The use of antihistamine therapy in patients with adenoid symptoms may be considered and should be further investigated. This treatment could be applied in all AH patients and continued for patients whose adenoid symptoms decrease after initial treatment.

Hypertonic saline solutions

This type of solution is used as an auxiliary and has been shown to be highly effective in cleansing the nasal mucosa of residual secretions and allergens. Hypertonic solutions are more effective in this respect; it is also important that the effectiveness in cleansing the mucosa increases with the volume of solution used (57). Such solutions should be used as a supportive treatment for adenoid symptoms.

Halotherapy

The release of micronized medical iodized sodium chloride in indoor climate-controlled conditions is another option for AH treatment. A study performed by Gelardi showed higher percentages of adenotonsillar tissue reduction in children after 10 daily sessions of micronized salt inhalation in a salt room when compared to placebo (58). This result was not statistically significant, however, and the authors concluded that a large sample of patients would be needed to show statistically significant rates of adenoid reduction.

Adrenomimetic agents

Although one study has shown the supporting effect of using oxymetazoline in AH treatment with nasal steroids, the lack of symptoms of rhinitis medicamentosa, and the rebound effect on the mucous membrane, most authors do not recommend their chronic use due to increasing rebound nasal congestion (50, 59).

Antibiotics

Even in the latest research by Zuo et al., it has been shown that the adenoid is a habitat for aerobic bacteria that can affect the development of AH, and the associated symptoms and appropriate antimicrobial therapy seem to be obvious (60). In the past, several weeks of antibiotic therapy have been used to treat AH, but this method was discontinued due to the negative impact of systemic antibiotic use on the entire microbiome of a child's body (44, 61). Currently, the local supplementation of bacteria to modify the nasal and nasopharyngeal microbiomes is more popular (62). Another approach is a 12-week treatment with OM85-BV, which may improve the Th1 immune response by weakening the local inflammatory response in the adenoids (63).

Proton pump inhibitors

Some studies have indicated a correlation between AH and gastroesophageal reflux, or AH and laryngo-pharyngeal reflux (64–67). Sagar demonstrated that adenotonsillectomy resulted in complete resolution of GER in 80% of children and improvement in 20% (66). However, in contrast, Iqbal's did not support the efficacy of PPIs for adenoid hypertrophy in children (68).

Anti-leukotriene therapies

Recently, some publications have pointed to the effectiveness of treating obstructive sleep apnea (OSA) with anti-leukotriene drugs for three months and adenoid hypertrophy (**Table 2**) (69–73). Ras showed better outcomes for oral montelukast with intranasal steroid in the treatment of AH than single-use mometasone (69). This is consistent with Tuhanoglu et al.'s findings, who described better symptom recovery in children treated with combined montelucast and mometasone furoate therapy; however, their objective assessment of adenoid size measured by lateral cephalometry showed no difference between this group and groups treated with mometasonel or montelucast

TABLE 2 Review of similar studies comparing effectiveness of anti-leukotriene therapy in children with adenoid hypertrophy. M: montelukast; MF: mometasone furoate.

Author year country	Age	Number of patients treated with montelucast/Control group	Medication	Time of treatment	Time of final result count	Main results
Ras (69) 2020 Egipt	3–10	50/50	M+MF Control MF	3 months	At the end of therapy, 3 months after treatment	Endoscopic A/C ratio examination Significantly better improvement over controls
Tuhanoglu (70) 2017 Turkey	4–10	30/30/30/30	M MF M+MF Placebo	3 months	At the end of therapy	Lateral cephalograms: Similar adenoid to air passage improvement in all groups, except placebo Best recovery in symptoms score in combined group
Shokouhi (71) 2015 Iran	4–12	30/30	M Placebo	3 months	At the end of therapy	Lateral cephalograms: Reduction of more than 25% in adenoid size in 76% treated patients vs. control (3.3%) Nasal endoscopy findings: Significant difference between groups after treatment
Liu (72) 2017 China	–	69/69	M+MF MF		At the end of therapy	M+MF more effectively reduced the adenoid nasopharynx ratio
Goldbart (73) 2012 Israel	2–10	23/23	M Placebo	3 months	At the end of the study	Lateral cephalogram radiography Decrease of the nasopharyngeal ratio in group treated with montelukast

alone (70). A study performed by Goldbart et al. showed that the adenotonsilar tissue of children with OSA contained higher leukotriene levels than that with infectious tonsilitis, and for this reason, this anti-leukotriene therapy should be applied to treat children with OSA symptoms rather than infectious adenoid symptoms (74). Montelukast is not approved for the treatment of AH and AR in Europe. Serious side effects, including hyperactive sleep disorders and depression, should be taken into consideration if anti-leukotriene therapy is to be applied (75, 76). Perhaps for this reason, all therapeutic regimens administered so far have lasted no longer than three months (**Table 2**).

Our single observations of patients treated with juvenile asthma with the use of leukotriene for a few years did not confirm its role in decreasing adenoid size. **Figure 3** shows an endoscopic view of an adenoid 8-year-old boy treated with 5 mg montelukast per day because of asthma for 3 years. Still, the role of anti-leukotriene therapies in decreasing adenoid size should be investigated.

In analysing the methods of conservative treatment described in the literature, there are still no spectacular effects or breakthroughs to be found. However, accurate diagnosis and clinical analysis should allow for the selection of patients who may be susceptible to medical treatment and able to avoid surgical treatment and related complications. Topical steroid treatment and saline irrigation should be applied before consideration of surgical treatment. Furthermore, antihistaminic drug and anti-leukotriene therapy studies should be analysed to evaluate possible benefits and side effects. Conservative treatment may be more effective with an A/C ratio beneath <75% (1–3 degrees of adenoid hypertrophy on the Cassano scale).

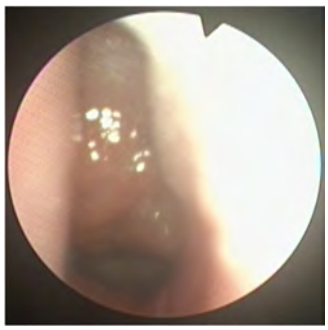

FIGURE 3
Endoscopic view of adenoid in 8-year-old boy treated with montelukast.

Is there an alternative treatment?

Some Chinese studies have indicated the efficacy of traditional Chinese herbal medicine for AH treatment in children, which showed better outcomes than Western medicine results (77–79). Zhao showed that oral Xiao-xian decoction combined with acupuncture (acupoint application) improved clinical symptoms of adenoid hypertrophy and may be suitable for long-term treatment (79).

However, there is still a variety of herbs mixtures used and no consensus on the treatment methods, as well as a lack of objectively evaluated measurements (80). Therefore, there is a need for long-term prospective clinical trials and a necessity to carry out evidence evaluation on the treatment of AH with Chinese or Western medicine to provide feasible and effective treatment options for clinics (78).

Acupuncture

Similar to Zaho's reports, the case presented by Deng showed the effectiveness of sphenopalatine ganglion electroacupuncture in widening the patency of the nasopharyngeal space in a 9-year-old boy (79, 81). While these are interesting reports, they do require further medical analysis.

What factors may influence the assessment of the effectiveness of conservative treatment?

To properly assess the effects of treatment, a questionnaire assessing the effects should be standardised. The proposed questionnaire is presented in **Table 3**. The child's parents should evaluate the change in symptoms and illness, such as snoring,

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TABLE 3 Proposed standardised questionnaire for children suspected of adenoid hypertrophy.

First visit Date: Comments:								Control Months after first visit:						
								1–3	3–6	7–9	9–12			
								The proposed conservative treatment was applied:						
								Yes			No			
								Overall improvement:						
								Yes			No			
Season of visit	Winter/autumn			Summer/spring				Winter/autumn			Summer/spring			
Adenoid surgery	yes			no				yes			no			
Allergy	Yes		No		Not tested			Yes		No		Not tested		
Snoring	Yes		Occasionally			No		Improvement		No improvement				
Open mouth	Yes		Occasionally		No			Improvement		No improvement				
Hypoacusis	Yes		Occasionally		No			Yes		Occasionally		No		
Rhinitis	Persistent		Seasonal			No		Improvement		No improvement				
Rhinitis - weeks per month	<1		1		2	3	4	<1		1	2	3	4	
Recurrent upper respiratory tract infections	yes				no									
Courses of systematic antibiotics during the previous 6 months	0	1	2	3	4	5	6	0	1	2	3	4	5	6

sleeping with the mouth open, apnoea, periods of rhinorrhoea, allergies, recurrent infections, hearing loss, or otitis media. The season in which the assessments are performed should also be taken into consideration when evaluating the effects of the treatment. Our research has shown that seasonality itself significantly affects the condition of adenoid mucus and tympanometry, but not adenoid size (46). The results of treatment should be analysed with the most objective tool; currently, the gold standard is flexible nasopharynx examination.

Surgical adenoid treatment: adenoidectomy

Sclafani et al. reported that 90% of children with AH underwent surgery in the two-year period after the initial diagnosis (61). Slightly fewer children (70%) were operated on in Circuoli's studies regarding the effectiveness of conservative treatment of AH with intranasal beclomethasone (43). In fact, adenoidectomy is one of the most frequently performed surgeries in children (82). Bleeding is the most dangerous complications after surgery. The rate of haemorrhage following adenoidectomy is one in 200 (0.5%); taking into consideration the number of treatments performed, this affects many children. Attention should also be paid to the possibility of less frequent complications and to the child's stress associated with the first surgery. For this reason, children qualified for surgery should be well diagnosed to avoid ineffective and unjustified treatment (83). For example, adenoidectomy is recommended for the treatment of chronic rhinosinusitis in children. However, the effectiveness of adenoidectomy in chronic rhinosinusitis treatment in preschool and early-school children reaches only 47%–58% (84, 85). This could be attributed to the lack of normalised conservative treatment and appropriate diagnosis and qualification for surgery. In many cases, conservative therapy may allow time for the proper action of drugs on the adenoid and adenoid symptoms and maturation of the immunology system of the child.

Adenoid tissue regrowth after surgery may occur in 31.3% of operated children, especially those younger than five years of age (81). Such regrowth may cause a recurrence of symptoms. Some medical failures of adenoid surgery are caused by incomplete resection, whereas others can be attributed to persistent infections of the upper respiratory tract, asthma, gastroesophageal reflux (GERD), and AR (86, 87). Some of these illnesses can be diagnosed early and conservatively treated. Regrowth rate also depends on the surgeon's experience and applied surgical technique (86, 88). Yildirim showed that "blind curettage adenoidectomy" may leave up to 18% of a large residual adenoid. For total adenoid tissue resection, the nasopharynx should be controlled during the surgery by posterior rhinoscopy with the use of a mirror or trans-nasally with the use of an endoscope (88). Additionally, a study performed by Pagella et al. indicated that a greater length of the soft palate corresponds to a great risk of remnant adenoid tissue, with the authors suggesting a procedure with endoscopic control be performed, regardless of the surgical technique (89). Specifically, the authors recommended endoscopic control if the soft palate length is greater than 2.5 cm (89). The most important purpose of adenoid surgery is to precisely resect the adenoid tissue without leaving any macroscopic remnant. This increases the likelihood of resolving clinical problems related to AH. Compliance with these recommendations is expected to bring the overall rate of revision adenoidectomy down from 1.6% to 2.5% (87, 90).

Conclusion

The diagnosis of AH should be widely based on flexible endoscopy, and other newly introduced diagnostic methods should

be connected to this method. There is still no unified conservative treatment schema for AH or consensus on the length of treatment. In this respect, further research and a determination of the effects of different medical curations are indicated. Bearing in mind the fact of slow reduction of the hypertrophic adenoid under the influence of drugs, when undertaking conservative treatment, long-term therapy should be considered, with consideration of the side effects of the drugs used. The results of the treatment should be related to the most effective adenoid visualization method, which is flexible endoscopy and with the use of the Cassano and MASNA scales. Conservative therapy may be more effective when the A/C ratio remains <75%. In properly qualified patients, surgical treatment will be effective, provided that the adenoid tissue is radically resected, which is significantly more successful through intraoperative endoscopic control.

Author contributions

Conceptualization, AZ; methodology, AZ and KD; software, KD; validation, AZ and KD; formal analysis, AZ and KD investigation, AZ resources, AZ; data curation, AZ; writing—original draft preparation, AZ; writing—review and editing, KM; visualization, KM; supervision, PB; project administration, AZ. All authors contributed to the article and approved the submitted version.

Conflict of interest

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.

Publisher's note

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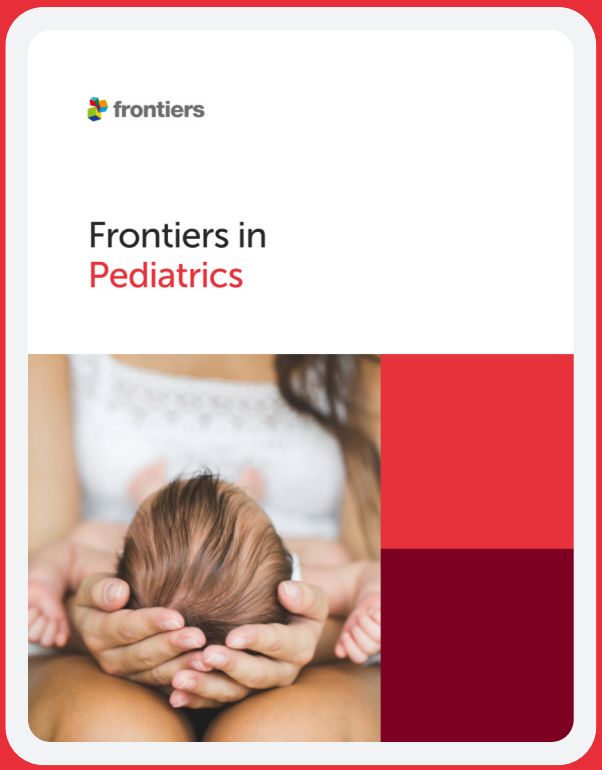

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