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Inflammatory cytokines in pediatric obstructive sleep apnea

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Abstract

Pediatric obstructive sleep apnea (OSA) is associated with chronic systemic inflammation and with cognitive impairments. This study aimed to investigate the status of proinflammatory cytokines, particularly interleukin 17 (IL-17) and interleukin 23 (IL-23) and cognition in pediatric OSA.

Controls and OSA children participated in the study. Exclusion criteria were adenotonsillectomy, heart, neurological and severe psychiatric diseases, craniofacial syndromes, and obesity. Polysomnogram was followed by serum testing for inflammatory markers and neurocognitive tests such as continuous performance task (CPT) and Wisconsin card sorting test, questionnaires, analyses of plasma high-sensitivity C-reactive protein (HS-CRP), tumor necrosis factor alpha (TNF-α), interleukin 1 (IL-1), interleukin 6 (IL-6), IL-17, and IL-23.

Seventy-nine, 4 to 12-year-old subjects in 2 groups ended the study: 47 nonobese OSA children (mean age = 7.84 ± 0.56 years, body mass index [BMI] = 16.95 ± 0.47 kg/m^2, BMI z-score = 0.15 ± 0.21, and mean apnea–hypopnea index [AHI] = 9.13 ± 1.67 events/h) and 32 healthy control children (mean age = 7.02 ± 0.65 years, with BMI = 16.55 ± 0.58 kg/m^2, BMI z-score = −0.12 ± 0.27, and mean AHI = 0.41 ± 0.07 event/h) were enrolled. Serum cytokine analyses showed significantly higher levels of HS-CRP, IL-17, and IL-23 in OSA children ($P = 0.002$, $P = 0.024$, and $P = 0.047$). Regression test showed significant influence of HS-CRP, TNF-α, IL-6, IL-17, and specifically IL-23, with the continuous performance test and Wisconsin card sorting test.

OSA children have abnormal levels of IL-17, an interleukin related to T helper 17 cells, a T helper cell involved in development of autoimmunity and inflammation. This high expression level may contribute to the complications of pediatric OSA; we also found a significant influence of inflammatory cytokines, particularly IL-23, on abnormal neurocognitive testing.

Abbreviations: ADHD = attention deficit–hyperactivity disorder, AHI = apnea–hypopnea index, BMI = body mass index, CPT = continuous performance task, EEG = electroencephalogram, EMG = electromyogram, Hit RT ISI = change hit reaction time interstimulus interval change, Hit SE ISI = change hit standard error interstimulus interval change, Hit-RT = hit reaction time, HS-CRP = high-sensitivity C-reactive protein, IL-1 = interleukin 1, IL-10 = interleukin 10, IL-17 = interleukin 17, IL-23 = interleukin 23, IL-6 = interleukin 6, k-CPT = Conners Kiddie continuous performance test, OSA = obstructive sleep apnea, PSG = polysomnogram, RDI = respiratory disturbance index, SaO_2 = oxygen saturation, TH17 = T helper 17 cells, TNF-α = tumor necrosis factor alpha, Treg = T-regulatory, WCST = Wisconsin card sorting test, WPPSI-R = Wechsler R intelligence test.

Keywords: inflammatory cytokines, interleukin-17, interleukin-23, neurocognitive functions, pediatric obstructive sleep apnea

1. Introduction

Obstructive sleep apnea (OSA) syndrome affects the sleep and neurocognitive functioning of children,[1–4] including symptoms of attention deficit–hyperactivity disorder (ADHD).[3–4] Pediatric OSA results in long-term effects on children's health and development.[5–7] The factors involved in the decrease in cognition, learning, and memory are still incompletely chartered.

1.1. Pediatric OSA and inflammatory cytokines

There is an interaction between OSA and chronic diseases.[8–10] The most acceptable hypothesis associates occurrence of chronic systemic inflammation with OSA.[11–12] Increase in proinflammatory cytokines (C-reactive protein [CRP], tumor necrosis factor alpha [TNF-α], interleukin 6 [IL-6], and interleukin 10 [IL-10] in adult OSA patients, and high-sensitivity C-reactive-protein [HS-CRP] in pediatric OSA patients) supports this hypothesis,[13–15] with a possible association between the apnea–hypopnea index (AHI) and inflammatory cytokine levels. The inflammatory responses may be reversed after OSA treatment.[16–18] In the recent past, advances in our understanding of the precursors of some of the measured cytokines have occurred. Also very recently, the discovery of functional lymphatic vessels lining the dural sinuses and expressing the molecular hallmarks of lymphatic endothelial cells and carrying

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fluid and immune cells from the cerebrospinal fluid with connection to the cervical lymphatic nodes has been reported.[19]

The proinflammatory cytokines, interleukin 17 (IL-17) and interleukin 23 (IL-23), have been recently emphasized. IL-17 is a proinflammatory cytokine secreted predominantly by T helper 17 cells (TH17) and various cells including innate immune cells and nonimmune cells.[15] It is referred to as IL-17A as it is a member of the IL-17 family.[20] The IL-17-producing cells secrete IL-17A and another family member, IL-17F, under the stimulation of cytokines such as IL-1, IL-6, and IL-23 secreted by antigen-presenting cells in response to antigen stimulation.[20,21] The interaction is as follows: IL-17A and IL-17F form homodimers or heretodimers that bind to the IL-17 receptor complex on inflammation-related cells such as macrophages, epithelial cells, and endothelial cells.[22,23] The activated inflammatory cells produce various cytokines including IL-1, IL-6, and TNF-α. The stimulation of these cytokines and inflammatory cells leads to inflammatory responses such as neutrophil recruitment, tissue destruction, and neovascularization. The overreacted immune responses resulted in autoimmune diseases and allergy. During inflammation, expression of IL-17 and IL-17F is upregulated,[22,23] with expression of high levels of IL-17 in patients with severe allergy, chronic inflammatory diseases, and autoimmune diseases.[23,24] IL-17 also takes part in neutrophilic inflammation in the respiratory system,[24,25] and leads to chronic inflammation of the airway[25]; for example, there is high expression level of IL-17F in asthma.[26] IL-17 has been linked to adult OSA: there is an upregulated Th17/T-regulatory (Treg) cell ratio and an overexpression of IL-6 and IL-17 in plasma cytokine suggesting that the imbalance of Th17/Treg and the microenvironment created by oversecreted proinflammatory cytokines contribute to the development of OSA.[27] In OSA children, cytokine profile obtained from tonsils shows high levels of IL-1b, IL-10, and IL-17A production, indicating a T-cell activation in response to inflammation.[28]

IL-23 is a cytokine with immunomodulatory effects.[29] It acts on memory-cluster–designation-4 (+) T cells, activates the transcription activator, and stimulates the production of interferon-gamma.[30,31] Studies showed that TH17 cells can be regulated by IL-23.[32]

Factors leading to cognitive changes in children with OSA are still subject of research: sleep fragmentation, hypoxemia, hypercapnia, and change in cerebral blood flow may be involved. Inflammatory cytokines may also play a role. We investigated interleukins 17 and 23 and cognition changes in children; we hypothesized that chronic inflammation not only causes cardiovascular diseases in pediatric OSA patient, but also affects cognitive functions and wondered if a correlation between psychometric test and these cytokines could be shown.[15] A study found a relationship between abnormal level of C-reactive protein and cognitive dysfunction in school-aged children but investigation of interleukins 17 and 23 will give a much more important view on the inflammatory status present in children with OSA and potential correlations with specific cognitive testing.

We prospectively examined whether the plasma levels of the inflammatory cytokines are altered in children with pediatric OSA related to enlarged T&A and we simultaneously surveyed the changes of neurocognitive tests: we investigated the potential relationship between increase in inflammatory cytokines and neurocognitive functions investigated by psychometric tests,[33] correlating the level of CRP, TNF-α, IL-1, IL-2, IL-6, IL-10, IL-17, and IL-23 with polysomnogram (PSG) results and neurocognitive test findings.

2. Methods

2.1. Inclusion/exclusion

Children aged 4 to 12 years and their parents were prospectively approached. They were either presenting with complaints and symptoms of pediatric OSA (as defined in the International Classification of Sleep Disorders-2-2005) or had no sleep-related or other symptoms (controls). Subjects were investigated at Chang Gung Memorial University Hospital (CGMH) after approval of the protocol by the institutional review board of CGMH (no. 103-0601C). All caregivers (parents) signed an informed consent. Two groups of participants were collected—group A: normal control (n = 32) and group B (n = 47) pediatric OSA with sleep disturbances.

Obesity, previous adenotonsillectomy craniofacial anomalies, neuromuscular diseases, and other neurological and psychiatric disorders, presence of chronic medical problems, and intelligence quotient (IQ) < 70 defined as mental retardation were the exclusion criteria. In addition, children unable to cooperate with blood withdrawal collection and PSG procedures were eliminated from the study. Obesity was defined based on Taiwan general public health tables.

Inclusion criteria were either presence of signs and symptoms evoking OSA for at least 3 months with confirmation by polysomnography-PSG-findings (AHI greater than 1 event/h or respiratory disturbance index (RDI) more than 5 events/h) (OSA group) or absence of complaint, AHI < 1, and presence of a noninflammatory status (absence of asthma, allergies, eczema, or other atopic/autoimmune diseases: normal control).

2.2. Procedures

(1) All subjects underwent routine medical history and physical examination by otolaryngologist, craniofacial surgeon, pediatrician, and child psychiatrist assessing comorbidities.
(2) Demographic data (age, sex, height, and weight) and all systemic comorbidities were collected on a standardized data sheet.
(3) Tonsillar size was graded by specialists following standardized scale from 0 to +4. Adenoid tissue was examined with a lateral x-ray film of the neck and flexible endoscope with amount of obstruction categorized into 4 grades (from grade 0 = 0%–25% to grade 3 = 75%–100%). Allergic rhinitis was confirmed by a specific IgE blood test (ImmunoCAP 100; Phadia, Uppsala, Sweden), and duration and persistence of symptoms and comorbidities according to the Allergic Rhinitis and its Impact on Asthma classification.
(4) Polysomnography (PSG): The following variables were monitored: electroencephalogram (EEG) (4 leads); eye movement, chin, and leg electromyogram (EMG); electrocardiogram (1 lead); and body position. The respiration was recorded with nasal pressure transducer, mouth thermocouple, chest and abdominal inductive plethysmography bands, neck microphone, diaphragmatic–intercostal muscle EMGs, and pulse oximetry from which both oxygen saturation (SaO_2) and finger plethysmography were derived, data were collected on a 32-channel recording system, (Embla N7000-Covidien, Kanata, Ontario, Canada), with continuous video monitoring. A family member was present during the nocturnal recording. Sleep and wake were scored using international criteria[33] with identification of stages 3 and 4. EEG arousal was defined according to the American Sleep Disorders Association.[34] Abnormal breathing events during

Table 1

Interleukin ELISA kits and minimum detection dose for assay.

ELISA kits	
R&D systems, Minneapolis, MN	**Minimum detection dose for assay**
IL-1β (DLB50)	Less than 1 pg/mL
IL-6 (HS600B)	0.447–9.96 pg/mL
IL-10 (D1000B)	Less than 3.9 pg/mL
IL-17 (D1700)	Less than 15 pg/mL
IL-23 (D2300B)	2.7–16.3 pg/mL

ELISA = enzyme-linked immunosorbent assay.

sleep were analyzed using the definitions of apnea and hypopnea as outlined by the American Academy of Sleep Medicine,[35] and the definition of flow limitation with abnormal increase in respiratory effort leading to arousals as outlined by Guilleminault et al.[36] The AHI and the RDI (number of apneas, hypopneas, and respiratory effort–related arousals per hour of sleep) were calculated. PSG scoring was performed by a technician blinded to the clinical status of the child.

(5) Inflammatory cytokine assessment: Blood samples were collected and allowed to clot for 30 minutes. The samples were then centrifuged, and the serum was frozen at −70 °C until assay. All samples were collected the morning after PSG. The serum levels of HS-CRP, TNF-α, IL-1β, IL-6, IL-10, IL-17, and IL-23 were determined by commercially available ultrasensitive enzyme-linked immunosorbent assay kits (R&D systems, Minneapolis, MN) (Table 1). There were duplications of each sample, and the mean was used as the unit of analysis for statistical evaluation of data. The Stem-and-leaf analysis (SPSS, Inc., Chicago, IL) was employed in order to test for extreme outlying cytokine result.

2.3. Questionnaire evaluations and neurocognitive tests

Following PSG, 4 subjective questionnaires were filled out by caregivers to evaluating sleep quality and quality of life of children including the obstructive sleep disorder questionnaire, children's sleep habits questionnaire, and child behavior checklist.

Evaluation of neurocognitive function was carried out using the Wechsler-R intelligence (WPPSI-R) intelligence test for 3- to 6-year-old children, WPPSI-R for 6- to 16-year-old children to assess IQ score, the Conners' Kiddie Continuous Performance Test (k-CPT) for 4- to 7-year-old children (k-CPT), the continuous performance test (CPT) that measures the subject's attention problem in 3 domains: inattention; impulsivity, vigilance, and retention ability; and the Wisconsin card sorting test for children assessing executive functioning ability.

The results of CPT score are presented in T scores. High T scores indicate an attention problem, with any T score >60 considered as abnormal. The high T score of omissions, commissions, hit reaction time (Hit RT), Hit RT std. error, variability, detectability, Hit RT interstimulus interval change (Hit RT ISI change), and Hit standard error interstimulus interval change (Hit SE ISI Change) indicate inattention; while commission, Hit RT, and perseveration indicate impulsivity; and Hit RT block change and Hit SE block change indicate vigilance.

The Wisconsin card sorting test (WCST) measures the subject's executive function. The total errors scores is an overall score of WCST, and higher score indicates worse performance. "Perseverative response" and "error-T score" are higher in subjects with worse performance of mental flexibility and insight. "Non-perseverative error" reflects difficulty to forming concepts and insight even in flexible answer. Conceptual-level response score indicates the insights in correct principle of card combination. "Learning to learn" depicts the average tendency over successive categories for efficiency to change.

Table 2

Demographic characteristics of OSA and healthy children.

	Control (n = 32)	OSA (n = 47)	*P*
Number of males, %	21 (65.6%)	30 (63.8%)	0.428
Age, y	7.02 ± 0.65	7.84 ± 0.56	0.366
BMI, kg/m^2	16.55 ± 0.58	16.95 ± 0.47	0.601
BMI z-score*	−0.12 ± 0.27	0.15 ± 0.21	0.442
AHI, events/h	0.37 ± 0.06	9.13 ± 1.67	<0.001§
PLMI, events/h	0.13 ± 0.10	0.93 ± 0.41	0.067‖
PLM disorder, %	0 (0%)	3 (6.4%)	0.083‖
Learning disorder, %†	0 (0%)	1 (2.1%)	0.461
ADHD, %†	2 (6.2%)	18 (38.3%)	0.001¶
Enuresis, %†	4 (12.5%)	15 (31.9%)	0.036#
Other physical comorbidity history			
Asthma, %‡	4 (12.5%)	6 (12.8%)	0.561
Allergic rhinitis, %‡	4 (12.5%)	23 (48.9%)	<0.001§
Findings of ENT examination			
Tonsil hypertrophy (more than Gr. 2), %‡	4 (12.5%)	32 (68.1%)	<0.001§
Adenoid hypertrophy, %‡	3 (9.3%)	24 (51.1%)	<0.001§
Turbinate hypertrophy, %‡	1 (3.1%)	6 (12.8%)	0.158
Nasoseptal deviation, %‡	0 (0%)	1 (2.1%)	0.461

* Corrected BMI z-score based on the center for disease control growth charts.
† Diagnosed according to the criteria of diagnostic and statistical manual of mental disorders. Fourth edition-text revision.
‡ Diagnosed by pediatricians.
§ $P < 0.001$. ADHD = attention deficient–hyperactivity disorder, AHI = apnea–hypopnea index, BMI = body mass index, ENT = ear, nose, and throat, OSA = obstructive sleep apnea, PLM = periodic limb movement, PLMI = periodic limb movement index.
‖ $0.05 \leq P < 0.1$.
¶ $P < 0.01$.
# $P < 0.05$.

2.4. Statistical analysis

The data are shown as means ± standard deviation. Student *t* tests were used to compare the findings in the OSA and control group. Taking into consideration the size of our group which limits usage of specific statistics such as "a mixed effects model", we used the "standardized regression test" much better suited which was performed to demonstrate the relationship of cytokines levels with PSG and neurocognitive outcomes after controlling the factors of "asthma, allergy, body mass index (BMI), gender, tonsil hypertrophy, adenoid hypertrophy, turbinate hypertrophy, and nasoseptal deviation". All the reported *P* values are 2-tailed with statistical significance set at <0.05. Statistics were performed with SPSS version 18.

3. Results

Eighty-two children, 3 to 12 years old, were enrolled; there were 3 dropouts (3.6%). Demographics of the 78 children (mean age 7.43 ± 0.6 year) are in Table 2. The OSA group was significantly different with symptoms of ADHD and enuresis ($P = 0.001$ and 0.036), presence of tonsil and adenoid hypertrophy ($P < 0.001$), BMI, and BMI z-score ($P = 0.001$ and 0.036). The PSGs showed

Table 3

Comparison of polysomonogram findings in OSA and healthy children.

	Control (n = 32)	OSA (n = 47)	*P* value
BMI, kg/m^2	16.55 ± 0.58	16.95 ± 0.47	0.601
BMI z-score	−0.12 ± 0.27	0.15 ± 0.21	0.442
Polysomonograhic findings			
AHI, events/h	0.37 ± 0.06	9.13 ± 1.67	<0.001*
AHI/REM, events/h	0.65 ± 0.18	16.25 ± 3.68	<0.001*
AI, events/h	0.18 ± 0.05	2.12 ± 0.51	0.001†
Desaturation index, events/h	0.41 ± 0.06	7.27 ± 1.59	<0.001*
Sleep efficiency, %	89.70 ± 1.32	83.65 ± 2.28	0.131
Awake, %	6.74 ± 1.42	10.90 ± 2.36	0.305
REM, %	18.62 ± 1.406	19.11 ± 1.16	0.820
Stage N1, %	10.46 ± 1.70	10.24 ± 1.44	0.935
Stage N2, %	41.65 ± 2.67	42.56 ± 2.74	0.853
Stage N3, %	28.28 ± 2.71	30.40 ± 1.28	0.434
TST, min	405.26 ± 10.96	383.34 ± 11.15	0.274
Sleep latency, min	17.67 ± 3.84	20.86 ± 3.74	0.629
PLM index, events/h	0.13 ± 0.10	0.93 ± 0.41	0.067‡
Snore index, events/h	30.41 ± 15.28	156.02 ± 35.62	0.002†
Mean SaO_2, %	95.97 ± 1.12	90.12 ± 3.61	0.332
Systolic pressure	100.80 ± 17.20	106.76 ± 19.40	0.387
Diastolic pressure	60.00 ± 22.36	66.79 ± 11.86	0.141

* $P < 0.001$. AHI/REM = AHI during REM, AHI = apnea–hypopnea index, AI = apnea index, BMI = body mass index, lowest SaO_2 = lowest oxygen saturation, mean SaO_2 = mean oxygen saturation, OSA = obstructive sleep apnea, PLM = periodic limb movement, REM = rapid eye movement, SPT = sleep period time, TIB = time in bed, TST = total sleep time, WASO = wake time after sleep onset.
† $P < 0.01$.
‡ $0.05 \leq P < 0.1$.

(Table 3) significantly higher AHI, AHI in rapid eye movement, apnea index (AI), desaturation index, and snore index in OSA children ($P < 0.001$, $P < 0.001$, $P = 0.001$, $P < 0.001$, and $P = 0.002$, respectively). In addition (Table 4), the expression of inflammatory cytokines IL-17, IL-23, and HS-CRP was significantly elevated in children with OSA ($P = 0.002$, $P = 0.024$, and $P = 0.047$, respectively). Plasma levels of TNF-α, IL-1, IL-6, and IL-10 showed a nonsignificant elevation compared with normal control. Results of CPT and WCST tests (Table 5) indicated significant difference between OSA and control in "Hit-RT-Std.-Error" ($P = 0.006$) and "hit reaction time (Hit-RT)-ISI-change" ($P = 0.004$).

A standardized regression test was performed to demonstrate the relationship of cytokine levels with PSG and neurocognitive outcomes after controlling the factors of asthma, allergy, BMI, gender, tonsil hypertrophy, adenoid hypertrophy, turbinate hypertrophy, and nasoseptal deviation (Tables 6 and 7). It revealed significant relationship between proinflammatory cytokines and some PSG factors, such as HS-CRP with AI ($\beta = 0.390$, $P < 0.05$) and IL-17 with AHI severity ($\beta = 0.329$, $P < 0.05$) (Table 6). Higher AI "influenced" serum levels of HS-CRP suggest an impact of inflammatory cytokines on soft tissues hypertrophy. Similarly, higher serum levels of IL-23 was "influenced" by higher AI ($\beta = 0.403$, $P < 0.05$). Also, lower mean SaO_2 "influenced" IL-10 level ($\beta = -0.567$, $P < 0.01$) and

Table 4

Comparison of inflammatory cytokines in healthy and OSA children.

	Control (n = 32) (mean ± SD)	OSA (n = 47) (mean ± SD)	*P*
HS-CRP, mg/L	0.41 ± 0.48	1.90 ± 0.44	0.002*
TNF-α, μg/dL	12.62 ± 0.94	12.58 ± 0.83	0.974
IL-1β, pg/mL	0.42 ± 0.27	0.36 ± 0.16	0.857
IL-6, pg/mL	1.10 ± 0.18	1.66 ± 0.23	0.104
IL-10, pg/mL	2.10 ± 0.28	2.62 ± 0.39	0.332
IL-17, pg/mL	10.20 ± 1.25	15.12 ± 1.38	0.024†
IL-23, pg/mL	12.29 ± 0.73	14.58 ± 0.75	0.047†

HS-CRP = high-sensitivity C-reactive protein, IL-1β = interleukins 1 beta, IL-10 = interleukin 10, IL-17 = interleukin 17, IL-23 = interleukins 23, IL-6 = interleukin 6, OSA = obstructive sleep apnea, TNF-α = tumor necrosis factor alpha.
* $P < 0.01$.
† $P < 0.05$.

Table 5

Comparison of CPT and WCST findings in OSA children.

	Control total (n = 32)	OSA total (n = 47)	*P*
CPT			
Clinical confidence index	39.34 ± 15.91	49.51 ± 24.46	0.142
Omissions T score	46.57 ± 5.36	52.33 ± 17.93	0.074*
Commissions T score	40.50 ± 10.93	45.03 ± 13.02	0.237
Hit RT T score	49.94 ± 8.86	57.08 ± 13.03	0.056*
Hit RT std. error T score	45.79 ± 6.26	52.96 ± 12.23	0.006†
Variability T score	46.43 ± 7.31	51.42 ± 10.57	0.099*
Detectability T score	40.87 ± 12.39	54.62 ± 15.72	0.316
Response style T score	51.57 ± 14.97	53.12 ± 14.69	0.732
Perseverations T score	49.69 ± 7.91	55.34 ± 12.25	0.104
Hit RT block change T score	48.99 ± 6.54	50.43 ± 6.73	0.479
Hit SE block change T score	49.40 ± 7.71	50.07 ± 11.00	0.831
Hit RT ISI change T score	47.88 ± 5.25	54.53 ± 10.83	0.004†
Hit SE ISI change T score	46.80 ± 8.80	51.70 ± 9.06	0.077*
WCST			
Total errors standard scores	107.20 ± 20.97	99.67 ± 24.26	0.392
Total errors T scores	54.80 ± 13.97	49.81 ± 16.19	0.395
Perseverative responses T scores	55.10 ± 14.77	50.56 ± 16.57	0.452
Perseverative errors T scores	56.30 ± 15.10	50.74 ± 16.42	0.357
Nonperseverative errors T scores	55.60 ± 14.37	52.78 ± 16.66	0.639
% Conceptual level response T scores	54.50 ± 4.60	50.19 ± 3.31	0.487
Learning to learn	−3.49 ± 11.66	−3.90 ± 9.78	0.712

CPT = continuous performance task. The result of CPT score is presented in T scores. According to the Conners CPT Computer Program User's Manual, high T scores are designed to indicate an attention problem. Any T score above 60 is considered abnormal. The confidence index presents the summary of the CPT. The omissions reveal the number of targets which the person did not respond to. The Commission reveals the number of times when the person responds to a non-target. Hit RT = hit reaction time; which reflects the mean response time. Hit RT std. Error = hit reaction time standard error; which measures the speed consistency. The variability, also a measure of response time consistency, which calculates the standard deviation of the 18 standard error values calculated for each sub-block. The detectability is a measure of discriminative power. The higher response style T score indicates that the person act more cautiously to avoid commission error, and the lower score indicates that the person respond more freely to make sure they answer most of the target. The perseverations T score shows the frequency when responding time is lower than 100 milliseconds. Hit RT block change = hit reaction time block change. The Hit RT block change shows the change in reaction time over the 6 time blocks; the higher Hit RT block change T scores indicates a slowing of reaction time as the test progress. Hit SE block change, Hit standard error block change, which indicates the consistency the person react to the targets as test progress. Hit RT ISI change = hit reaction time inter-stimulus interval change, reflects the change in reaction time over three inter-stimulus intervals (1, 2 and 4 seconds.) Higher score reflects slowing of reaction time as the intervals between targets increased. Hit SE ISI change = hit reaction time inter-stimulus interval change. Higher score reflects the person became more erratic as the time between targets increased, OSA = obstructive sleep apnea. WCST = Wisconsin card sorting test. The total errors scores is an overall score of WCST test, and the higher raw score indicates worse performance. The perseverative response and error raw score are higher in the person with worse performance of mental flexibility and insight. The non-perseverative error reflects difficulty to forming concepts and insight even in flexible answer. The conceptual level response score indicates the insights in correct principle of the card combination. Learning to learn depicts the average tendency over successive categories for efficiency to change.
* $0.05 \leqq P < 0.1$.
† $P < 0.01$.

Table 6

Relationships between inflammatory cytokines and PSG findings.

	HS-CRP	TNF-α	IL-1β	IL-6	IL-10	IL-17	IL-23
Polysomonographic data							
AHI severity[*,†]	0.237	−0.078	0.026	0.124	0.205	0.329[‡]	0.184
AHI, events/h[*]	0.114	−0.109	−0.114	−0.095	−0.079	0.059	0.163
AHIREM, events/h[*]	0.022	−0.101	−0.095	−0.082	−0.027	0.095	0.331[§]
AI, events/h[*]	0.390[‡]	0.162	−0.209	−0.074	−0.31[§]	−0.238	0.403[‡]
HI, events/h[*]	0.020	−0.100	−0.129	−0.036	0.080	0.225	0.276
Desaturation index, events/h[*]	0.156	0.076	−0.151	−0.088	−0.147	0.001	0.317[§]
Sleep efficiency, %[*]	−0.037	0.041	−0.090	0.050	−0.150	−0.126	−0.077
Awake, %[*]	−0.016	0.012	0.059	−0.046	0.139	0.089	0.054
REM, %[*]	0.111	0.064	0.057	0.318[‡]	0.026	0.148	−0.090
Stage N1, %[*]	0.022	−0.168	0.076	−0.011	0.139	−0.086	0.183
Stage N2, %[*]	−0.520	−0.174	−0.049	0.001	−0.220	0.026	−0.234
Stage N3, %[*]	−0.261	−0.061	0.057	−0.189	0.330[‡]	0.191	−0.206
TST[*]	0.118	−0.057	−0.27[§]	0.188	−0.224	0.034	0.067
Sleep latency[*]	0.162	−0.141	0.297[‡]	0.014	0.092	0.012	0.133
PLM index[*]	−0.048	0.088	−0.006	−0.141	−0.201	−0.33[‡]	0.230
Snore index[*]	−0.079	−0.145	0.133	−0.052	0.066	0.157	−0.052
Mean SaO_2, %[*]	0.040	−0.159	0.012	−0.123	−0.57[‖]	−0.242	−0.023
Systolic pressure[*]	−0.43[§]	0.064	0.09	−0.41[§]	−0.14	0.088	−0.56[‡]
Diastolic pressure[*]	−0.15	0.47[‖]	0.66[‖]	−0.18	−0.10	−0.10	−0.06

[*] Standardized regression coefficient. Control factors: asthma, allergy, body mass index, gender, tonsil hypertrophy, adenoid hypertrophy, turbinate hypertrophy, nasoseptal deviation.

[†] AHI severity: $5 \geq AHI > 1$ events/h (mild), $10 \geq AHI > 5$ events/h (moderate), $AHI > 10$ events/h (severe); AI = apnea index, HI = hypopnea index, HS-CRP = high-sensitivity C-reactive protein, mean SaO_2 = mean oxygen saturation, PLM = periodic limb movement, REM = rapid eye movement, TNF-α = tumor necrosis factor alpha, TST = total sleep time.

[‡] $P < 0.05$.

[§] $0.05 \leq P < 0.1$.

[‖] $P < 0.01$. AHI, apnea-hypopnea index.

higher serum levels of TNF-α and IL-1β were "influenced" by higher diastolic pressure (β = 0.469 and 0.659, $P < 0.01$).

There was a significant relationship between lower performances of CPT test and proinflammatory cytokines as shown in Table 7. The standardized regression test indicated significant findings between proinflammatory cytokines and neurocognitive function tests. The elevated cytokines are related to domains of inattention, vigilance, such as "Hit-RT-ISI-Change T score" and

Table 7

Relationships between inflammatory cytokines and neurocognitive function tests.

	HS-CRP	TNF-α	IL-1β	IL-6	IL-10	IL-17	IL-23
CPT							
Clinical confidence index[*]	−0.185	−0.177	−0.040	−0.027	0.181	0.424[†]	−0.317
Omissions T score[*]	−0.256	−0.154	−0.067	−0.109	0.002	0.112	−0.336[‡]
Commissions T score[*]	0.037	0.075	0.170	0.030	0.250	−0.056	0.045
Hit RT T score[*]	−0.071	−0.127	0.006	−0.106	0.065	0.267	−0.249
Hit RT std. error T score[*]	−0.207	−0.216	0.083	−0.103	0.182	0.294[‡]	−0.322[‡]
Variability T score[*]	−0.247	−0.098	0.160	−0.009	0.354[‡]	0.274	−0.291
Detectability T score[*]	−0.116	0.032	0.136	−0.004	−0.050	−0.186	0.034
Response style T score[*]	−0.044	−0.432[†]	−0.101	−0.039	0.136	0.309[‡]	−0.129
Perseverations T score[*]	−0.253	0.109	−0.013	−0.112	0.155	0.184	−0.203
Hit RT block change T score[*]	−0.146	−0.328[†]	−0.066	−0.017	0.105	−0.102	−0.051
Hit SE block change T score[*]	−0.100	−0.121	0.131	−0.029	0.201	−0.184	−0.051
Hit RT ISI change T score[*]	−0.426[†]	−0.155	0.003	−0.168	−0.012	−0.036	−0.545[§]
Hit SE ISI change T score[*]	−0.389[†]	−0.192	0.174	−0.159	0.049	0.114	−0.526[§]
WCST							
Total errors standard scores[*]	−0.123	−0.335	0.089	0.436[‡]	0.065	−0.086	−0.443[‡]
Total errors T scores[*]	−0.124	−0.345	0.082	0.433[‡]	0.068	−0.083	−0.446[‡]
Perseverative responses T scores[*]	−0.276	−0.093	0.186	0.324	−0.016	0.027	−0.179
Perseverative errors T scores[*]	−0.262	−0.117	0.175	0.324	−0.021	0.012	−0.197
Nonperseverative errors T scores[*]	0.047	−0.553[†]	−0.058	0.255	0.106	−0.250	−0.729[§]
% Conceptual level response T scores[*]	−0.131	−0.315	0.067	0.476[†]	0.081	−0.079	−0.404[‡]
Learning to learn[*]	0.336	−0.838[†]	0.019	0.221	0.119	0.330	0.295

[*] Standardized regression coefficient. Control factors: asthma, allergy, body mass index, gender, tonsil hypertrophy, adenoid hypertrophy, turbinate hypertrophy, and nasoseptal deviation.

[†] $P < 0.05$.

[‡] $0.05 \leq P < 0.1$.

[§] $P < 0.01$. CPT = continuous performance task, Hit RT ISI = change hit reaction time interstimulus interval change, Hit SE ISI = change hit standard error interstimulus interval change, HS-CRP = high-sensitivity C-reactive protein, TNF-α = tumor necrosis factor alpha, WCST = Wisconsin card sorting test.

Table 8

Correlations between inflammatory cytokines and comorbidities.

	HS-CRP	TNF-α	IL-1β	IL-6	IL-10	IL-17	IL-23
Comorbidity							
Learning disorder*	0.186	0.060	0.045	0.123	−0.201	−0.093	
ADHD*	0.070	−0.114	0.031	−0.019	0.138	0.191	−0.153
Enuresis*	0.068	0.044	−0.027	0.182	−0.185	0.101	−0.078
Other physical comorbidity							
Asthma*	0.201	−0.084	0.075	0.261†	−0.189	−0.061	−0.197
Allergic rhinitis*	0.280†	−0.079	0.101	0.299†	−0.265†	0.044	−0.005
Findings of ENT examination							
Tonsil hypertrophy (more than Gr. 2)[b]	0.244†	0.132	0.035	0.175	−0.156	0.070	0.137
Adenoid hypertrophy*	0.196	−0.037	0.108	0.232†	−0.141	0.064	0.025
Turbinate hypertrophy*	0.003	0.173	−0.020	0.083	−0.026	0.249†	−0.084
Nasoseptal deviation*	−0.013	0.037	0.045	0.006	−0.140	−0.093	0.128

* Spearman correlation.

† $P < 0.05$. ADHD = attention deficient–hyperactivity disorder, HS-CRP = high-sensitivity C-reactive protein, TNF-α = tumor necrosis factor alpha.

HS-CRP ($\beta = -0.426$, $P < 0.05$); "Response-Style T score", and TNF-α ($\beta = -0.432$, $P < 0.05$); "Hit RT ISI Change T score" and "Hit SE ISI Change T score" with IL23 ($\beta = -0.545, -0.526$, $P < 0.01$); and higher "Confidence-Index" with IL17 ($\beta = 0.424$, $P < 0.05$). When looking at the influence between inflammatory cytokines and WCST, the results indicate that elevated cytokines, such as TNF-α and IL6, are related to decrease of executive functions such as "non-Perseverative Errors T scores" ($\beta = -0.553$, $P < 0.05$); "Learning-to-Learn" ($\beta = -0.838$, $P < 0.05$); and "Percent-Conceptual-Level-Response T scores" ($\beta = 0.476$, $P < 0.05$); especially IL-23 with significant poor performance of "non-Perseverative-Errors T scores" ($\beta = -0.729$, $P < 0.01$).

Table 8 shows the significant Spearman correlation factors between proinflammatory cytokines and clinical findings such as asthma and IL-6 ($\rho = 0.261$, $P = 0.026$); allergic rhinitis and HS-CRP ($\rho = 0.280$, $P = 0.022$*), IL-6 ($\rho = 0.299$, $P = 0.01$*), and IL-10 ($\rho = -0.265$, $P = 0.023$*); tonsil hypertrophy and HS-CRP ($\rho = 0.244$, $P = 0.046$); adenoid hypertrophy and IL-6 ($\rho = 0.232$, $P = 0.048$*).

In summary, our study showed that an abnormal increase in interleukins 17 and 23 is present in association with mild-to-moderate OSA in prepubertal children. Lower neurocognitive test results are also demonstrated in the OSA children, and there are significant positive correlations between low scores at cognitive tests (showing decreased alertness and increase in inattention, inability to focus leading to erratic responses, and to appropriately conceptualize) and abnormal level of inflammatory cytokines, more particularly IL-17 and IL-23.

4. Discussion

Plasma levels of proinflammatory cytokines such as HS-CRP, TNF-α, IL-1β, and IL-6 have been previously reported as elevated in children with OSA; and the expression ratio of the IL-10 and IL-6 was elevated in OSA children with recovery after adenotonsillectomy surgery.[17] This last finding supported the concept that OSA induces a systemic inflammatory response activating the signal transduction pathway leading to upregulation of inflammatory cytokines and downregulation of anti-inflammatory cytokines.

But the interaction between the different cytokines may not be as clear-cut as thought, the advances in the recognition of the activation of a chain of inflammatory factors allow further understanding. We found a nonsignificant trend toward elevation of IL-10 in our subjects: as this cytokine is involved in both pro- and anti-inflammatory processes, further investigations will be needed.

Also, although IL-6 has no significant high expression level in our OSA children, we cannot exclude a role for IL-6 in OSA-related inflammation, as IL-6 is a crucial cytokine signal in guiding the differentiation of naïve T cells into TH17 cells that release IL-17. But there may be other pathways leading to secretion of IL-17: as for example, IL-23 is a key cytokine and one of its reported activity is to differentiate naïve T cells into IL-17-producing TH17 cells.[31] But IL-17 could also be produced without intervention of IL-23.[37–39] Independent of the interaction between the different inflammatory interleukins, the fact remains that IL-17 is abnormally and significantly elevated in children with OSA. Overall, IL-17 acts in synergy with TNF-α, triggering the signaling pathway that upregulates the downstream cytokines, IL-6 and IL-8. In the animal model of autoimmune arthritis,[40,41] it was shown that IL-17 itself stimulates the cellular production of IL-1 and TNF-α. In addition, IL-17 ultimately leads to recruitment of inflammatory cells such as neutrophils and other leukocytes.[42] In summary, all of the above studies confirmed that IL-17, primarily secreted by TH17, a subset of T helper cells, is a proinflammatory cytokine that acts with the company of other cytokines such as IL-1, TNF-α, and IL-6 to induce systemic inflammatory diseases and plays an important role in the development of autoimmunity. Our study indicates that both IL-17 and IL-23 are elevated in pediatric OSA and could be used as biomarkers of pediatric OSA. They can play a role in the development of secondary health problems noted with OSA.

OSA not only affects cardiovascular functions and growth problem but also causes behavioral and cognitive dysfunction in children.[43] But the mechanisms involved are still unknown. Evidence suggests that some peripheral proinflammatory cytokines such as IL-1 and IL-6 can go through the blood–brain barrier.[15,44] The new finding in rodent of a direct connection between cerebrospinal fluid and deep neck lymph nodes is also a very important clue.[19] These cytokines activate and regulate the vagus nerve system, and this activation affects the function of central nervous system.[44,45] Moreover, chronically rising level of proinflammatory cytokines may also induce neuroinflammation or neurodegeneration and cause impairment of neurocognitive functions.[46,47] Other research shows reduction of cognitive function as related to increased level of peripheral IL-6 even in the normal-aging Americans.[48,49] Our study shows that higher levels of TNF-α and IL-23 are significantly related to some

neurocognitive deficits in pediatric OSA. New studies should further address this issue.

Our study has limitations: despite the fact that we looked at 79 children, even if a high number for this type of study, this is still an overall low number. Also, our controls were somewhat "hyper-normal": we eliminated from the study any child who had an indication of abnormal levels of inflammatory cytokines; finally, our children were not all with "severe" OSA (only 17% had AHI > 10), all however presented abnormal PSG findings. In addition, our findings are in line with data showing that even children with low but abnormal AHI have often memory problems, attention problems, and school difficulties.[3–6] Finally, as the total number of children is relatively limited, despite the usage of "standardized regression test" before performing correlation analyses and the inclusion of all studied children for statistical purpose, the results will need to be confirmed with larger numbers and/or evaluation of change noted with appropriate treatment.

OSA in children impacts brain functioning: cognitive, memory, attention disorders, as well as behavioral and mood problems are much more common than any other listed complications. The impact of inflammatory factors, neuroinflammation, and dysfunction of the neuronal network has been mentioned by many; our study indicates that specific and unreported up-to-now interleukin abnormalities (IL-17 and IL-23) may be present very early in association with sleep disorder breathing; these proinflammatory cytokines may be potential markers helping in diagnosis and post-treatment follow-up of pediatric OSA.

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