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Interleukin 8 in children with obstructive sleep apnea before and after adenotonsillectomy

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Abstract

Objective To assess serum interleukin 8 (IL-8) levels after adenotonsillectomy in children with symptoms suggestive for OSA.

Study design Prospective interventional study.

Settings The study was carried out on 30 children with OSA attending ENT clinic of Suez Canal University Hospital.

Methods Including, children with sleep-related chronic intermittent hypoxia (CIH) and OSA symptoms performed an elective adenotonsillectomy, and aged (3–12 years). Excluding, children with acute tonsillitis, cardiorespiratory, craniofacial, or diseases affecting IL-8 level as cystic fibrosis, COVID-19 patients, and hepatitis C, taking drugs affecting IL-8 level as benzodiazepines or glutamine supplementation. Children were subjected to full history, clinical examination and laboratory investigations. Nocturnal pulse oximetry (ChoiceMMed) was performed (48–72 h preoperative and 3–4 weeks postoperative) used to determine the number of 4% dips in saturation from baseline, and the nadir saturation (nSAT). IL-8 was measured 1 month pre-operative and 1 month post-operative by flow cytometry using the Human Inflammatory Cytometric Bead Array kit.

Results The mean preoperative IL-8 (237.55 p/ml) and oxygen desaturation index (7.77%)cwere statistically significantly higher than mean postoperative IL-8 (207.98 p/ml) and oxygen desaturation index (2.90). The mean pre-operative SpO2 is 98.27 ranged (96.00–100.0%), while the mean postoperative SpO2 is 98.77 ranged (97.00–100.0%), with no statistically significant difference between them ($p=0.069$). Preoperative IL-8 (p/ml), postoperative IL-8 (p/ml), and preoperative SpO2 (%) were found to be negatively correlated with IL-8 change.

Conclusion IL-8 level significantly decreased after adenotonsillectomy in children with symptoms suggestive for OSA.

Keywords OSA, Adenotonsillectomy, Children, Inflammatory markers, IL-8

Background

Recurrent episodes of interrupted breathing during sleep and repeated oxygen desaturation episodes in the blood are the two main characteristics of obstructive sleep apnea (OSA) [1].

The prevalence of obstructive sleep disordered breathing (SDB) in children is extremely high. It is more common in children between the ages of 2 and 8, most likely as a result of the relative size of lymphoid tissue in contrast to the diameter of the airway. Primary

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snoring in children is reported to affect 4 to 12% of children [2].

Previous research determined that 7.45% of parents reported snoring overall. Based on several cross-sectional studies, prevalence estimates for OSA documented by polysomnography (PSG) in the general pediatric population have consistently ranged from 1 to 5% [3].

Significant harmful effects of untreated, severe OSA affect children's wellbeing and academic performance [4]. Adenotonsillectomy (T&A) is still the advised first line treatment for severe pediatric OSA, and adenotonsillar hypertrophy is thought to be the most common cause of this condition [5].

As the T&A surgery is associated with both morbidity and mortality, the indication for the surgery in mild cases of OSA is controversial. Clinical decisions could be influenced by an accurate biomarker for OSA severity [6].

About 300,000 ambulatory adenotonsillectomy procedures are carried out annually in children aged 15 or younger in the USA, making it one of the most common surgical procedures performed on children [7].

A previous study in the USA revealed that exclusive indications for surgery involved obstructed breathing of any type in 59% of cases, recurrent infections in 42%, and OSA in 39% of children. This suggests that obstructed breathing has overtaken recurrent infection as the most common surgical reason for an adenotonsillectomy [8].

Clinical research has concentrated on the relationship between serum or plasma biomarkers and OSA severity or outcomes [9]. Although cells like monocytes are known to be vulnerable to hypoxia, the effect of cellular alteration(s) in severe OSA has not received as much attention [10].

Ke et al. [11] evaluated the production of classic inflammatory cytokines in ex vivo cultures of isolated peripheral blood mononuclear cells (PBMC) collected from children with severe OSA who displayed sleep-related chronic intermittent hypoxia (CIH). It was concluded that in young children with sleep-related CIH, an enhanced production capacity of interleukin 8 (IL-8) occurs before the emergence of systemic inflammatory markers.

IL-8 is considered to be a chemokine which is formed by macrophages and other cell types as airway smooth muscle cells, epithelial cells, and endothelial cells. The Weibel-Palade bodies and associated storage vesicles are where endothelial cells keep IL-8 [12].

By activating nuclear transcription factor-KB, pro-inflammatory mediators including intercellular adhesion molecule 1 (ICAM-1) and IL-8 facilitate neutrophil attachment to endothelial cells as a result of OSA-induced overnight hypoxic stress [13].

There are a number of proxy indicators of subclinical inflammation that have been identified, including IL-8 and ICAM-1 in OSA, the former of which raises cardiovascular risk. However, further research is needed to understand the precise relationship between inflammation and cardiovascular events, as OSA is acknowledged as a serious public health concern due to its relation to an elevated risk of cardiovascular issues [14].

OSAS and hypoxia both increase IL-8 expression and production. The nightly hypoxic stress caused by recurrent OSAS may promote neutrophil adherence to endothelial cells [15].

So, this study was carried out to measure serum IL-8 level after adenotonsillectmy in children with symptoms suggestive for OSA.

Methods

Design

Prospective interventional study.

Setting

The study was conducted in ENT clinic of Suez Canal University Hospital, Ismailia City, Egypt.

Selection criteria

Our study included children with symptoms of OSA, with sleep-related CIH, children who underwent an elective T&A, and aged 2–12 years. Excluded children with acute tonsillitis (fever > 38.3 °C, cervical lymphadenopathy (tender or enlarged (> 2 cm) lymph nodes), tonsillar or pharyngeal exudate, positive culture for group A β-hemolytic streptococcus), with a history of cardiorespiratory, neurologic, craniofacial, immunodeficiency, or genetic disorders, having diseases affect IL-8 level as cystic fibrosis, nosocomial bacterial infections, COVID-19 and patients with severe disease taking drugs affect IL-8 level as benzodiazepines, taking glutamine supplementation.

Sample size

Sample size was 30 children with OSA, taken with purposive sampling technique. It was determined using data from a previous study in which the mean IL-8 preoperative and postoperative values were 5.6 and 11.7, respectively [16].

The following procedures were applied to all patients: A thorough medical history was taken, along with clinical information on the patient's age, weight, height, gender and body mass index (BMI). A nocturnal pulse oximetry study (ChoiceMMed) was carried out (48–72 h prior to surgery and 3–4 weeks following surgery) to count the number of 4% dips in saturation from baseline and the nadir saturation (nSAT). Parents were instructed on how to conduct overnight oximetry testing correctly. The

oximeter was brought home by the parents, used for the study, and then brought back to our sleep laboratory [17].

Laboratory investigations

Isolation and stimulation of peripheral blood mononuclear cells (PBMC): within 4 h after blood collection, PBMC were extracted from heparinized whole blood using density gradient centrifugation (Ficoll-Paque PLUS, GE Healthcare Bio-science AB, Uppsala, Sweden). Two milliliters of plasma samples were obtained and then kept at − 80 °C in microcentrifuge tubes. Lipopolysaccharides were used to activate PBMC in vitro for 24 h at 37 °C with 5% CO2 and normoxia. Centrifugation was used to collect the culture supernatants, which were then chilled to − 80 °C before being used. We measured the baseline cytokine production in unstimulated PBMC.

Cytometric bead array for measuring cytokine production: using the Human Inflammatory Cytometric Bead Array kit, flow cytometry was used to measure the amounts of cytokines in the plasma and culture supernatants (BD Biosciences, Mississauga, Ontario, Canada). The kit provided simultaneous quantification of (IL-8) with sensitivity comparable to that of conventional ELISA. One month before surgery and 1 month after surgery, IL-8 levels were assessed [15].

Statistical analysis

SPSS® Statistics version 25 was used for all data manipulation and analysis (IBM Corporation, Armonk, NY, USA). Every graph was made with Microsoft® Excel. The mean, standard deviation, and range were used to represent continuous variables in analyses. The terminology for categorical variables was frequencies and percentages (%). The Kolmogorov–Smirnov test was used to determine the normality of continuous variables. Given that the continuous variables were not normally distributed, Mann–Whitney and Kruskal–Wallis tests were utilized. To check for correlation between continuous variables, Spearman's rank correlation was used. A p value of 0.05 or less was regarded as statistically significant.

Ethical consideration

Before collecting any data or conducting any physical examinations on children, informed consent was collected from their guardians/caretakers and was approved by the research ethical committee of the Suez Canal University faculty of medicine. The patients' participation was voluntary because they were free to decline without giving a reason. Patients were informed that the confidentiality of their data was maintained. Consent was expressed in writing.

Results

The study results have revealed that the mean age of our study participants is 7.67, ranged 3–12 years, the mean weight is 23.68 ranged 15–31 kg, the mean height is 114.79 ranged 93–131 cm, the mean BMI is 18 ranged 16–28 kg/m^2, the majority of our study participants (60%) were males, while only (40%) were females, the mean duration of complaint is 2.93 ranged 1–5 months.

Table 1 shows the preoperative and postoperative sleep time of the studied sample, the mean preoperative sleep time is 6.68 ranged from 4.50 to 9.25 min, the mean postoperative sleep time is 6.60 ranged from 4.75 to 8.75 min, with no statistically significant difference between them ($p = 0.142$).

The mean preoperative IL-8 (237.55 p/ml) is statistically significantly higher than mean postoperative IL-8 (207.98 p/ml), ($p < 0.001$) (Table 2).

Table 3 shows that the mean pre-operative SpO2 is 98.27 ranged 96.00–100.0%, while the mean postoperative SpO2 is 98.77 ranged 97.00–100.0%, with

Table 1 Preoperative and postoperative sleep time of the studied sample

All patients ($n = 30$)	Mean and SD	Median	Range	IQR	*P*
Preoperative sleep time (minutes)	6.68 ± 1.206	6.75	4.50, 9.25	5.69, 7.25	0.142
Postoperative sleep time (minutes)	6.60 ± 1.213	6.75	4.75, 8.75	5.50, 7.25	

P <0.05 is significant

Table 2 Preoperative and postoperative IL-8 assessment of the studied sample

All patients ($n = 30$)		Mean and SD	Median	Range	IQR	*P*
IL-8 (p/ml)	Preoperative	237.55 ± 90.460	245.10	72.00, 420.20	177.98, 287.83	< 0.001
	Postoperative	207.98 ± 78.337	215.95	63.40, 371.60	159.45, 244.08	

P <0.05 is significant

Table 3 Preoperative and postoperative oxygen saturation and oxygen desaturation index of the studied sample

All patients ($n=30$)		Mean and SD	Median	Range	IQR	*P*
SpO2 (%)	Preoperative	98.27 ± 0.944	98.00	96.00, 100.0	98.0, 99.0	0.069
	Postoperative	98.77 ± 1.073	99.00	97.00, 100.0	98.00, 100.0	
Oxygen desaturation index	Preoperative	7.77 ± 3.645	7.00	3.00, 19.00	5.00, 9.00	< 0.001
	Postoperative	2.90 ± 1.954	2.00	1.00, 8.00	1.00, 4.00	

P <0.05 is significant

Table 4 Correlation between IL-8 change across study and other studied variables the studied sample

All patients ($n=30$)	Correlation coefficient	*P*
Age (years)	− 0.247	0.189
Weight (kg)	− 0.170	0.370
Height (cm)	− 0.014	0.940
BMI (kg/m^2)	− 0.111	0.559
Duration of complaint (months)	− 0.080	0.673
Preoperative sleep time (minutes)	− 0.101	0.595
Postoperative sleep time (minutes)	− 0.128	0.501
Preoperative IL-8 (p/ml)	− 0.925	< 0.001
Postoperative IL-8 (p/ml)	− 0.899	< 0.001
Preoperative O2 (%)	− 0.413	0.023
Postoperative O2 (%)	0.132	0.485
Preoperative oxygen desaturation index	− 0.202	0.284
Postoperative oxygen desaturation index	− 0.259	0.167

P < 0.05 is significant

no statistically significant difference between them ($p=0.069$). The mean preoperative oxygen desaturation index (ODI) (7.77%) is statistically significantly higher than the mean postoperative ODI (2.90) ($p<0.001$).

Preoperative IL-8 (p/ml), postoperative IL-8 (p/ml), and preoperative SpO2 (%) were found to be negatively correlated with IL-8 change (Table 4).

Discussion

Basic snoring to more severe variants, such as OSA, which is the second most prevalent respiratory condition after asthma in terms of prevalence, make up the spectrum of diseases known as SDB in children [18].

Our study results revealed that, the mean age of our study participants was 7.67, ranged 3–12 years, the mean weight is 23.68 ranged 15–31 kg, the mean height is 114.79 ranged 93–131 cm, the mean BMI is 18 ranged 16–28 kg/m^2), the majority of our study participants (60%) were females, while only (40%) were males. The mean duration of complaint is 2.93 ranged 1–5 months, about 63.3% had history of allergic disease and 13.3% of our study participants had a history of using corticosteroids. In our study, there was no statistically significant difference between the preoperative and postoperative sleep time (minutes).

In agreement with a study by Kheirandish-Gozal et al. [19], there was no significant difference between preoperative and postoperative sleep time (minutes). Additionally, there was no significant difference between preoperative and postoperative sleep efficiency in the study of Walker et al. [20].

Chemokine IL-8 is essential for both angiogenesis and the host immunological response, according to Russo et al. [21]. Adult OSA patients have been observed to have higher levels of inflammatory markers including IL-8. Similar to this, recent investigations have shown a link between childhood OSA and increased inflammatory mediators [22].

According to Metinko et al. [23], oxidative stress and anoxic preconditioning led to an increase in IL-8 production in monocytes. In this setting, it was discovered that OSA increased systemic inflammatory markers like IL-6 and IL-8 and that it also changed antiatherogenic cytokines like IL-10 in a reciprocal manner.

In the Ohga et al. [24] study, untreated OSAS patients had considerably higher circulating levels of IL-8 than did controls. In addition, Andersson et al. [25] showed that human tonsils with chronic infection led to more production of 19 distinct cytokines, including IL-1ß, IL-4, IL-6, IL-8, and TNF-a. Also, Li et al. [26] study's findings showed that children with OSA had higher IL-8 concentrations.

However, Tam et al. [27] was unable to demonstrate significantly elevated levels IL-8 in children with OSA after correction for age, sex, and BMI. This study's OSA subjects tended to be younger than those in ours. The discrepancy between Tam et al. and our findings can be explained by the tendency of younger participants to have shorter disease duration and, thus, a reduction in the duration of the theoretical pro-inflammatory period.

In this study, IL-8 was significantly decreased after adenotonsillectomy. This is comparable to the studies of Kheirandish-Gozal et al. [19] and Huang et al. [28], in which IL-18 was significantly reduced after T&A.

After T&A, IL-8 considerably increased in the Ke et al. [11] study. Although cultivated under normoxic circumstances, it was hypothesized that the higher IL-8 production capability was influenced by the fact that the peripheral blood mononuclear cell samples were taken from children who had severe sleep-related CIH. As a result, the circulating mononuclear cells were preconditioned with CIH; however, the molecular mechanisms underlying the relationship between CIH from sleep and the generation of IL-8 are yet unknown. It was also conceivable to use alternative explanations for the enhanced IL-8 production capability, such as the stimulus causing tonsillar growth.

In our study, there was no statistically significant difference between preoperative and postoperative O2. But there was statistically significant difference between preoperative and postoperative oxygen desaturation index. Similar effects on respiratory control and an increase in SaO2 were seen following T&A in children with OSA by Kudoh and Sanai [29] and Chu and Li [30].

In Mitchell [31] study, when the cardiorespiratory parameters and sleep architecture for children with obstructive sleep apnea were compared before and after adenotonsillectomy, it was discovered that changes in mean oxygen saturation and the central apnea index were significant. The increases in average sleep duration, sleep efficiency, and the proportion of time spent in REM sleep, however, were not statistically significant.

After an adenotonsillectomy, Stewart et al. [32] looked at changes in both quality-of-life indices and sleep study figures in a sample of children between the ages of 6 and 12. In a prior cohort research, the mean preoperative apnea–hypopnea index (AHI) was 4.8 (range 1.0 to 75.8) and decreased to 3.16 postoperatively in a group of 16 children who had both preoperative and postoperative PSG data. The lowest oxygen saturation level rose from 82% preoperatively to 91% after surgery. Nine out of 17 were discovered to be OSA-free.

We acknowledge that there are some potential drawbacks in our study. First, our analysis was performed on a quasi-experimental (one group) study without a control group. Second, other inflammatory variables such TNF-a and IL-6, which are closely linked to the development of excessive daytime drowsiness, were not evaluated postoperatively. Over-night pulse oximetry does not substitute polysomnography as the gold standard test for OSA.

Conclusion

After adenotonsillectomy, IL-8 levels in children with obstructive sleep apnea showed statistically significant reduction.

Recommendations

Il-8 is advised to be used as a screening tool in addition to polysomnography (PSG), the gold standard diagnostic tool for OSA and pulse oximetry to assess OSA patient improvement following adenotonsillectomy. In OSA patients, it's crucial to understand that T&A frequently fails to produce the expected outcomes in these patients. Therefore, additional research is required to assess the metabolic and systemic inflammatory indicators in OSA children so that better treatments can be developed. Future studies should include PSG, more patients, and longer patient follow-up will allow us to emphasize the short- and long-term results for a better assessment of the surgical outcome.

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Authors' contributions

MR analyzed and interpreted the patients' data, monitored research activities, guiding the research process and manuscript preparation. ME had a major role in the surgical planning and data interpretation. AF assisted in research proposal and data interpretation. NI conducted the research activity including surgical procedures and laboratory investigation. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

Faculty of Medicine, Suez Canal University research ethical committee on 5/5/2021 number: 4563. Informed written consent to participate was obtained from the parents/guardians of patients under 16 years old.

Consent for publication

Written informed consent for the publication was obtained from the parents or legal guardians of children under 16.

Competing interests

The authors declare that they have no competing interests.

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