Focus on prevention and treatment of obstructive sleep disordered breathing in childhood

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Successful management of OSAS in obese children requires a combination of treatment modalities

In this issue of the European Respiratory Journal, treatment outcomes of obstructive sleep apnoea syndrome (OSAS) in obese community-dwelling children are reported by ALONSO-ÁLVAREZ et al. [1]. The results of the NANOS multicentre trial indicate that obese children have a high rate of persistent disease despite treatment with adenotonsillectomy, nutritional interventions or even nasal continuous positive airway pressure (CPAP). OSAS is the most severe form of obstructive sleep disordered breathing (SDB), which is a syndrome of upper airway dysfunction during sleep characterised by snoring and increased respiratory effort [2, 3]. A combination of one or more anomalies, such as adenotonsillar tissue hypertrophy, obesity, subtle or syndromic craniofacial abnormalities, or neuromuscular disease, contributes to increased upper airway resistance and pharyngeal collapsibility, predisposing to intermittent upper airway obstruction during REM and NREM sleep [2].

Successful treatment of OSAS in childhood improves outcomes

Successful treatment of intermittent upper airway obstruction during sleep is clearly accompanied by favourable effects on SDB-associated morbidity. A systematic review highlighted the reduced prevalence of enuresis post-adenotonsillectomy even in children with mild disease, while a meta-analysis of 10 studies involving children with SDB and adenotonsillar hypertrophy showed significant increases in weight and height z-scores post-treatment [4, 5]. The Childhood Adenotonsillectomy Trial (CHAT), a US multicentre controlled study, confirmed that early adenotonsillectomy leads to significantly larger increase in the weight velocity, weight z-score, body mass index (BMI) velocity, and BMI z-score than watchful waiting and supportive care [6]. In the same multicentre trial, greater improvements in quality of life measures were shown in children randomised to early adenotonsillectomy [7]. In addition, OSAS-related daytime sleepiness and impaired quality of life and behaviour as reflected by symptom items of the Paediatric Sleep Questionnaire predicted significant improvement postoperatively [8]. Most importantly, each five-unit postoperative reduction in the apnoea–hypopnoea index (AHI), or 5 mmHg decrease in the peak end-tidal CO₂, was accompanied by a mean drop in heart rate by 1 or 1.5 beats per minute, respectively, denoting less sympathetic nervous system activation [9].

The definition of successful treatment of OSAS varies between studies

In the NANOS study, three different polysomnographic indices have been used to diagnose OSAS (respiratory disturbance index, RDI; obstructive respiratory disturbance index, ORDI; and obstructive

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apnoea−hypopnoea index, OAHI) with cut-off values ranging between 1 and 3 episodes per hour, according to different definitions used in the paediatric literature [1]. The main feature distinguishing RDI from ORDI and OAHI is the inclusion or exclusion of central events [10]. Nevertheless, the importance of central apnoeas in otherwise healthy children with OSAS is uncertain. They are associated with fluctuations in heart rate and blood pressure during sleep, and central apnoea index decreased after adenotonsillectomy in both a published Australian study and in the NANOS trial [1, 11, 12].

Although the selected cut-off values above which RDI, ORDI or OAHI are considered abnormal vary between 1 and 3 episodes per hour, it should be noted that upper centiles of the frequency of respiratory events in asymptomatic children and the lower centiles in children with SDB overlap [13]. In addition, even children who snore without detectable apnoeas, hypopnoeas or gas exchange abnormalities (primary snoring) may manifest SDB-associated morbidity [14]. Therefore, the cut-off values selected for the definition of OSAS are somewhat arbitrary.

Treatment modalities for OSAS in childhood are usually implemented in a stepwise fashion

Treatment interventions for obstructive SDB are usually implemented in a stepwise fashion starting from the least invasive modality so that all abnormalities which predispose to intermittent upper airway obstruction during sleep are addressed and OSAS ultimately resolves [3]. One or more of the following modalities are usually offered: weight control; use of anti-inflammatory medications; adenotonsillectomy; orthodontic appliances or rapid maxillary expansion; CPAP or non-invasive positive pressure ventilation (NPPV); craniofacial surgery and tracheostomy [3].

Obese children with OSAS frequently have unfavourable response to treatment interventions

In the NANOS study, three different groups of children with OSAS have been formed in addition to controls and the potentially most efficacious single treatment was offered to each of them: obese participants with mild OSAS but no adenotonsillar hypertrophy (group 2) had supervised dietary modification; obese children with adenotonsillar hypertrophy and moderate-to-severe OSAS (group 3) underwent adenotonsillectomy; and patients with moderate-to-severe OSAS but no adenotonsillar hypertrophy (group 4) were treated with nasal CPAP. Not surprisingly, overall BMI decreased in those subjects whose mild OSAS resolved (group 2). However, 30% of obese children who underwent adenotonsillectomy (group 3) had a postoperative OAHI >1 episode per hour (persistent OSAS), a frequency similar to that reported in the CHAT study for obese participants, taking into consideration that the definition used for OSAS differed slightly from definitions employed in the NANOS study [15].

The unfavourable response of obese children with OSAS to adenotonsillectomy has been reported in the literature previously, but the responsible pathophysiological mechanisms have not been explored. While most children with SDB-associated failure to thrive achieve normal weight post-adenotonsillectomy, overweight and obese children are at risk of accelerated weight gain and late recurrence of OSAS after an early improvement at 6 weeks postoperatively [6, 16]. More specifically, in the CHAT study, overweight children with OSAS assigned to adenotonsillectomy had 2.5 times higher risk of becoming obese than participants in the watchful waiting arm and obese children with persistent OSAS in the NANOS study had an impressive mean postoperative increase in BMI z-score of 1.83 [6].

A limitation of the study by ALONSO-ÁLVAREZ et al. [1] is that children with persistent OSAS did not undergo systematic evaluation for subtle craniofacial abnormalities using cephalometry, eventually followed by appropriate interventions such as application of orthodontic appliances for dental malocclusion or rapid maxillary expansion for narrow maxillae [17, 18]. Thus, the contribution of craniofacial factors to persistent OSAS which are present in both obese and normal-weight children with SDB remains undefined. Of interest, one out of six children who were treated with CPAP had persistent OSAS, suggesting the need for further pressure titration or use of NPPV.

Can persistence of untreated OSAS, residual post-treatment OSAS or new-onset OSAS be prevented?

Since treatment of OSAS in obese children is challenging, the question arises whether its spontaneous resolution can be accelerated and incident cases be avoided. In the NANOS study, children with persistent mild OSAS had a significant increase in BMI during the period of dietary modifications [19]. Similarly, in the prospective Tuscon’s Children’s Assessment of Sleep Apnea Study (TuCASA), untreated participants with persistent OSAS or new-onset disease had increased risk for rising BMI percentile or development of obesity during transition from childhood to adolescence [20]. In a population-based cohort from Hong Kong, persistence of overweight/obesity status over an average period of 4.6 years was a significant
predictor of primary snoring progression to OSAS [21]. Hence, maintenance of normal weight, especially in children with snoring, may facilitate resolution of untreated or persistent post-treatment OSAS and may potentially prevent incident cases.

Another important finding of the current study by Alonso-Álvarez et al. [1] was that among 3–14 year-old obese children without SDB, presence of tonsillar hypertrophy was a risk factor for developing OSAS over the follow-up period of approximately 12 months [1]. Contrary to the traditional clinical belief, adenotonsillar tissue hypertrophy does not resolve with increasing age and adenotonsillectomy is necessary to treat OSAS in cases of upper airway obstruction caused by pharyngeal lymphoid tissue hypertrophy [22].

A familiar predisposition to adenotonsillar hypertrophy and OSAS has been described and it may be attributed to the enhanced expression of leukotriene biosynthetic enzymes in tonsillar tissue and the increased production of cysteinyl leukotrienes which augment the proliferation rate of tonsillar lymphocytes [23–25]. Hence, we propose that early recognition of children at risk of adenotonsillar hypertrophy and SDB (e.g. those with recurrent wheezing or family history of SDB or adenotonsillectomy) might allow an early therapeutic intervention with anti-leukotriene medications in order to prevent newly developed OSAS and the need for adenotonsillectomy [26–29].

The NANOS study and future research questions

As is common with every well-designed study, the NANOS multicentre trial creates more questions than answers. If adenotonsillectomy were combined with a weight control programme, what would its efficacy be? Would the postoperative addition of nasal corticosteroid or montelukast increase the frequency of OSAS resolution by reducing chronic nasal mucosa oedema? Would AHI improve in obese children with dental malocclusion or retrognathia following implementation of a weight-control programme and orthodontic interventions? What are the effects of successful treatment of OSAS on cardiometabolic outcomes in obese children? Long-term follow-up and further interventions in the participants of the NANOS multicentre trial may clarify some of these questions. This is critical for improving the management of SDB in childhood. In any case, owing to the multifactorial origin of SDB in children, the NANOS study strongly suggests using multimodal treatment. This is actually a shared characteristic between children and adults presenting with OSAS, particularly in the case of obesity [30].

References


