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The Status of Pediatric Obstructive Sleep Apnea in 2015: Progress? YES!! More Questions? Definitely YES!!

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Abstract Significant advances have been made in the context of pediatric obstructive sleep apnea (POSA) in the past several years, and are clearly shifting the paradigm in many of the aspects related to the clinical evaluation and treatment of this highly prevalent pediatric condition. This review highlights some of the most salient studies that have undoubtedly contributed to the shifts and evolution in our understanding of POSA. A comprehensive and integrative summary of the published research papers tackling the etiology of POSA, and its pathological sequelae will be presented along with recent updates in POSA diagnosis and treatment.

Keywords Pediatric obstructive sleep apnea · POSA · Pediatric conditions · Sleep apnea · Obstructive sleep apnea · Children · Sleep breathing disorders

Introduction

Obstructive sleep apnea in children (POSA) is one of the most common causes of sleep-disordered breathing in children with a prevalence estimated to range between 1–5.7 % [1]. It is characterized by intermittent obstruction of the upper airways, which can result in intermittent hypoxia, hypercarbia, increase in respiratory effort as illustrated by pronounced intrathoracic pressure swings and repeated arousals resulting in sleep fragmentation. There is now incremental evidence primarily derived from studies in adults suffering from OSA as well as from animal studies primarily focused on intermittent hypoxia or sleep fragmentation that the perturbations that characterize POSA result in the activation of pathological cascades that in turn impose wide ranging effects, ultimately impacting on patients' neurocognitive and behavioral, cardiovascular and metabolic systems. Importantly, the adverse consequences of POSA may not be confined to the child's immediate well-being and development, but may continue to be detrimental to the patients' long-term health into adulthood. The emphasis of this article is to review the latest research and developments in POSA, and how such work provides us with improved understanding of the phenotypic characteristics and variability of POSA, as well as evolving directions aimed at facilitating the diagnosis and treatment of POSA.

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Etiology of POSA

The pathophysiological mechanisms underlying POSA can be broadly classified into those that cause intrinsic upper airway narrowing (the most common being adenotonsillar hypertrophy and obesity) and those that result in increased upper airway collapsibility (e.g., neuromuscular diseases, airway inflammation, and obesity). Frequently, several factors can coexist in the same child, such that the situation in which markedly enlarged adenoids and tonsils in the absence of any evidence of sleep-disordered breathing is relatively as frequent as the one in which severe POSA is present in the absence of enlarged upper airway lymphadenoid tissues. Notwithstanding, it is now well accepted that

anatomical risk factors involving some degree of adenoidal and tonsillar hypertrophy along with increased upper airway collapsibility are likely present in younger otherwise healthy children. However, there is little data regarding adolescents, a transitional period in which the emergence of puberty, adipose tissue alterations, and associated hormonal changes begins the emergence of a clear gender dimorphism, particularly in regards to disease prevalence. Schwab et al. therefore sought to further identify the underlying anatomical risk factors for OSA in adolescents. They performed MRI scans of the upper airway in 137 teenagers aged 12–16 years and divided them into 3 groups, namely, obese adolescents with OSA, obese controls and lean controls [2••]. Obese adolescents with OSA had increased size of adenotonsillar tissues with concurrently smaller nasopharyngeal airways compared with both control groups. In most of the obese adolescents with OSA, the ratio of soft tissue to craniofacial space surrounding the airway was increased, and gender differences were also noted, whereby boys had larger tonsils, and girls had larger adenoids. These results suggest that adolescents with OSA have an anatomic risk profile more akin to that of children, rather than the prototypic airway characteristics usually seen in adults with OSA. Such findings have potential implications on adolescent OSA management strategies since they imply that either surgical removal or pharmacologically-induced atrophy of upper airway adenoids and tonsils may be preferable as the initial strategy rather than immediate implementation of CPAP therapy.

One potentially useful complement of information during evaluation of children at risk for POSA would be objective assessment of upper airway collapsibility. However, objective measurements of upper airway collapsibility are not yet widely available in clinical practice, since they are relatively complicated to perform, require the application of negative nasal pressure to the sleeping patient [3] or need onerous sophisticated equipment such as acoustic pharyngometry [4]. To overcome these obstacles, McGinley et al. aimed to identify surrogate markers of upper airway collapsibility by performing analyses of inspiratory flow patterns and attempted to derive flow limitation metrics while relying on the nasal cannula flow-pressure signal during standard PSG recordings [5•]. They compared in children with OSA and in those with primary snoring the percentage of time with inspiratory flow-limited breathing (%IFL), and maximal inspiratory airflow during flow-limited breaths (expressed as a percentage of peak inspiratory flow during non-flow-limited breathing during non-REM sleep; %VImax). There were no differences in either of these 2 measures in non-REM sleep, but in REM sleep, children with OSA exhibited a higher %IFL and lower %VImax which improved following adenotonsillectomy (AT). The authors interpreted these findings as evidence of decreased compensatory neuromuscular responses to upper airway obstruction during REM in the OSA group, but most importantly showed that some derivative of airflow signal representing a surrogate indicator of airway resistance can be obtained during polysomnographic recordings in children in a breath-by-breath manner. Of course, the study has limitations, in particular, the qualitative nature of the nasal cannula signal, such that quantitative changes in airflow can be markedly affected by mouth breathing and cannula displacement. However, the concept is innovative and clearly merits further validation as well as exploration of its inherent value in relation to the clinical phenotypic variance of POSA. Based on the aforementioned findings in adolescents, it will be important to use the noninvasive techniques described by McGinley and colleagues during PSG studies to further refine the responses to sleep states and to changes in collapsibility during the transition from childhood through adolescence to adulthood in both girls and boys.

Obesity and OSA

Given the increasing prevalence of childhood obesity around the world and the strong association between increased ponderal indices and POSA, one of the most important recent etiological studies published was the NANOS study. This cross-sectional, prospective multicenter study examined 248 obese children aged 3–14 years recruited from the community. It consisted of two phases with phase 1 assessing the prevalence and risk factors for POSA, while phase 2 examined the treatment outcomes in those identified to have POSA. The prevalence of POSA when defined as a OAHI ≥ 3/h TST was 21.5 %, though this increased to 39.5 % when a RDI ≥ 3/h TST was used (as per the previously published Spanish consensus guidelines) [6•, 7]. Adenoidal hypertrophy and tonsillar hypertrophy, identified on nasal pharyngoscopy, emerged as the most important risk factor for POSA. In phase 2, outcomes of 117 children out of the original group were reported [8••]. They were classified into 4 groups. In group 1, obese children without POSA, 21 % developed POSA on their follow-up PSG. In group 2, obese children with mild POSA without adenotonsillar hypertrophy, managed with dietary modification to encourage weight loss, improvements in the respiratory parameters emerged, and half of this cohort no longer had evidence of POSA at follow-up. The weight loss needed to achieve such an improvement was encouragingly small. Group 3 were obese children with moderate/severe OSA with significant adenotonsillar hypertrophy who underwent AT. Here, the severity of POSA improved post-AT, but 43.5 % still had residual POSA. Similar to previous studies [9], age emerged as a significant risk factor for residual POSA. The final group included obese children with moderate/severe POSA who did not have adenotonsillar hypertrophy and these patients were treated with CPAP with attendant difficulties in adherence and the need for substantial behavioral interventions for both implementation and

sustained use over time. Overall, the authors concluded that in younger obese children, the major influence appears to be adenotonsillar hypertrophy, with BMI—adipose tissue mass apparently operating as a POSA enhancer rather an a causal contributor. However in older children, obesity becomes a more prominent POSA determinant, and appears to be an independent causal factor.

Such findings were overall not surprising, considering that POSA and obesity are both conditions in which low grade systemic inflammation is generally present. When obesity and POSA coincide in the same child, there is accruing evidence that one will potentiate the effects of the other [10]. An examination of 100 obese children with POSA using a panel of plasma inflammatory markers measured before and after treatment with adenotonsillectomy, showed that when OSA was successfully treated, IL-6, IL-18, PAI-1, MCP-1, MMP-9, adropin, and leptin plasma levels decreased, whereas adiponectin levels increased. In contrast, these improvements were not seen in the 30 children whose post-operative OAHI remained ≥5/h TST, and in fact, leptin levels increased, rather than decreased [11•]. These findings not only demonstrate that in obese children, POSA amplifies the underlying systemic inflammatory pathways that have been a priori activated by obesity, but importantly, effective treatment of the POSA, results in improvements in the global inflammatory state. A most recent retrospective study further provided confirmatory evidence that the personalized trajectory of an inflammatory marker such as high sensitivity CRP in the context of AT treatment of POSA provides a robust predictor of residual post-operative POSA [12]. Thus, future studies implementing measurements of panels of relevant and previously validated inflammatory biomarkers may provide opportunities for establishment of robust surrogate reporters of POSA morbidity and also enable the identification of residual POSA.

OSA and Asthma

Another major area of recent investigation has been the association and potential interdependency and overlap between POSA in children with asthma. The presence of a potential association between asthma and POSA has been recognized for some time now. There is a higher prevalence of POSA in asthmatic children and treatment of the POSA in a group of poorly controlled asthmatics resulted in improved asthma control [13]. There was a high proportion of obese children in these cohorts, an observation that was overall anticipated considering that obesity is an important risk factor for OSA, and that similarly, an epidemiological link has been described between obesity and asthma, thereby suggesting an interplay between the 3 conditions. Both asthma and POSA are associated with airway inflammation. Indeed, asthma has also been identified as one of the risk factors for residual OSA post-AT [9].

The link between POSA and asthma was further examined by Bhattacharjee et al. who performed a database analysis of 13,506 children with asthma in the USA who underwent AT, and examined their asthma control the year before and the year after AT [14••]. In this study, a 30 % reduction in asthma exacerbations, a 25 % decrease in the number of asthma related emergency room visits, and a 36 % reduction in asthma-related hospital admissions emerged after AT in this large pediatric asthmatic population. In contrast, among the 27,012 age-, sex-, and geographically-matched control children with asthma who did not undergo AT, there was just a 2 % reduction in asthma exacerbations. As with any database analysis, the authors acknowledge the limitations of the study as well as the lack of information on obesity and ethnicity. Notwithstanding, the findings conclusively provide compelling and real life evidence that AT is associated with improved asthma control, such that delineation of the mechanistic pathways connecting asthma and POSA would not only be fascinating, but also provide the rationale and impetus for diagnostic and therapeutic algorithms. One of the current hypotheses linking POSA and asthma is obviously the united airway hypothesis [15]. At this stage, it is certainly biologically plausible that inflammation of the upper airway from OSA may exacerbate inflammation in the lower airways, and thus deteriorate asthma control, and that vice versa, exhaled condensate with higher concentration of inflammatory substances originating from the lower airways in poorly controlled asthmatics may facilitate the proliferation, expansion and inflammation of upper airway lymphadenoid tissues thereby promoting upper airway collapsibility and obstruction.

There is also accumulating evidence that environmental modifiers also play a role in phenotypic expression. For example, exposure to passive smoking has been shown to be an independent risk factor for habitual snoring in pre-school children with a dose-dependent relationship identified between urinary cotinine concentrations and frequency of snoring [16]. Environmental air quality has also more recently emerged as a significant contributor with the frequency of habitual snoring in school-aged children residing in neighborhoods with greatest air pollution being threefold higher compared to those who reside in neighborhoods with less air pollution [17]. Low family social economic status (either independently or linked to environmental air quality) has also been associated with an increased risk of POSA [18]. Finally, in the CHildhood AdenoTonsillectomy study (CHAT) which will be discussed in greater detail later in this review, African American ethnicity and environmental tobacco exposure were each found to be associated with an approximately 20 % increase in apnea hypopnea index (AHI) [19].

Consequences of POSA—The Phenomics of POSA

Pediatric OSA morbidities are multiple and involve the cardiovascular, metabolic and neurological systems, and somatic growth. In addition, nocturnal bladder control and urinary output are also potentially affected but will not be addressed here.

Cardiovascular Morbidity

Evidence of endothelial dysfunction has been demonstrated in children with POSA using a variety of methodologies to assess post-occlusive hyperemic responses [20–22]. However, not all children with OSA have evidence of endothelial functional impairments. Among those who do, the majority show resolution of the endothelial dysfunction following treatment with AT, yet endothelial dysfunction persisted in a subgroup with a strong family history of cardiovascular disease [20, 21]. Much research has focused on identifying the factors contributing to this phenotypic variation both in the presence of endothelial dysfunction and the lack of resolution after treatment. The severity of endothelial dysfunction is greater in children who are obese and also have POSA, compared to either condition in isolation, once again, suggesting the convergence of the deleterious consequences of obesity and OSA [23]. To what extent genetic and environmental factors confer protection or increase vulnerability [24], and whether there are surrogate plasma-derived markers of endothelial dysfunction [25] is now being actively sought. In this context, the ability to recruit endothelial progenitors for endothelial repair [26, 27•], numbers and function of T regulatory lymphocytes [28], epigenetic alterations in genes such as endothelial nitric oxide synthase as well as polymorphisms in nitric oxide synthase and endothelin gene families are some of the factors recently identified as determinants of the variance in endothelial function [29–31].

Neurobehavioral Morbidity

The impact of POSA on neurobehavioral development has been an area of active research for over now two decades, and yet conclusive evidence assigning a mechanistic role to POSA on the increased risk of cognitive and behavioral deficits that are routinely seen in cohorts of children at risk of sleep-disordered breathing is still lacking. Preliminary functional MRI data has revealed that children with POSA, show greater activity in the regions of the brain implicated in cognitive control, conflict monitoring, and attentional allocation in order to perform tasks at the same level as children without POSA even when their cognitive abilities are preserved [32]. Furthermore, when viewing empathy-eliciting scenarios, children with more severe OSA demonstrated less activity in the left amygdala.

Childhood Adenotonsillectomy (CHAT) Study

The most prominent study that examined neurobehavioral outcomes as the primary outcome of interest was the CHAT study. This was the first ever randomized controlled trial to compare AT with watchful waiting in the management of pediatric OSA in school-aged children. There were no differences between the two randomized groups, in terms of the primary outcome of the trial, i.e., change in the attention and executive-function score in the Developmental Neuropsychological Assessment [33••]. However, AT resulted in significant improvements in symptoms as well as parent-rated generic and OSA-specific quality of life measures [34]. It is important to note that due to ethical considerations, the children recruited only had mild OSA with no significant oxygen desaturations [35], were above 4 years of age and were only followed up for 7 months. Thus, generalizations to children of other ages and severities of POSA are not possible. Indeed, when Lau et al. studied 23 children with OSA who had more severe OSA than in the CHAT study (mean OAHI: 5.6/h TST) and compared them with 22 matched controls, the children with POSA performed less well in both the basic storage and central executive components of working memory in the verbal domain than the controls [36].

One of the potentially most interesting findings of the CHAT study was that of the children who did not undergo AT, 42 % had resolution of their POSA on follow-up PSG 7 months later. These were children with lower initial AHI and with waist circumference <90 % percentile [37•]. However despite normalization of their PSG AHI, only 15 % experienced symptomatic resolution and the independent predictors for such improvements included lower initial Pediatric Sleep Questionnaire and snoring scores.

Metabolic Morbidity

The metabolic morbidities of OSA in adults are now quite well recognized and include lipid profile alterations as well as insulin resistance and diabetic decompensation [38–45]. However, the picture of these associations in children has been remarkably blurry as pointed by the high level of inconsistent evidence. One of the reasons advanced for these discrepant findings may reside in differences in pubertal status and the presence of concurrent obesity in the cohorts studied. For example, when Redline at al studied predominantly post-pubertal adolescents, strong associations between POSA and the metabolic syndrome, as well as with individual metabolic parameters such as fasting insulin and HOMA emerged [46]. However, in pre-pubertal children, while POSA has been implicated in elevations in LDL cholesterol with concomitant decreases in HDL cholesterol [47], reduced insulin sensitivity was only seen when obesity was concurrently present. Interestingly, highly sensitive functional network analysis of

enriched gene sets in children with primary snoring revealed subtle alterations in insulin homeostatic mechanisms [48], suggesting that mild perturbations in sleep may already impose sub-clinical changes in peripheral tissue insulin receptor sensitivity. In mild-moderate cases without accompanying obesity, insulin sensitivity seems to be preserved, but presence of obesity does induce insulin resistance [47, 49–51]. Treatment, however, does seem to improve glucose homeostasis in both obese and non-obese children - a recent study from our group has demonstrated that AT in children with POSA improves insulin resistance, and the residual metabolic dysfunction is associated with the degree of adiposity, rather than that of residual POSA severity [52]. These changes were seen in both obese and non-obese children, suggesting that OSA is causally involved in creating an adverse metabolic state independent from obesity. Interestingly, baseline fasting insulin independently predicted post-AT AHI, raising the possibility that IR per se could potentially exacerbate POSA. These results underscore the importance of a multidisciplinary approach when addressing the metabolic health in a patient with POSA, in addition to treatment of the underlying gas exchange and sleep perturbations associated with the disease.

There is emerging evidence of end-organ morbidity secondary to metabolic dysregulation. Two recent studies revealed that POSA/nocturnal hypoxemia is present in as many as 60 % of obese children with biopsy proven non-alcoholic fatty liver disease (NAFLD). The severity of the OSA/duration of the hypoxemia were associated with biochemical and histological features of NAFLD severity, independent of BMI, abdominal adiposity, metabolic syndrome, and insulin resistance [53]. Furthermore, the percentage of time with oxygen saturation ≤90 % correlated with increased intrahepatic leukocytes, activated Kupffer cells and circulating markers of hepatocyte apoptosis and fibrogenesis [54•]. The mechanisms underlying these findings were examined by Alkhouri et al., who showed that plasma levels of sFas and sFasL were lower in obese children with OSA compared with those without OSA [55]. Furthermore, sCD163 levels correlated with OSA severity and in the subgroup of patients who were treated for OSA, sCD163 levels decreased significantly. The significance of these findings is that Fas and FasL are part of the extrinsic apoptosis pathway, and their soluble forms are considered inhibitors of apoptosis because they effectively compete with the binding of FasL to Fas on the cell membrane, thereby suggesting higher levels of hepatic cellular apoptosis in POSA obese children. Meanwhile, sCD163 is a marker of macrophage activation and has been shown to be associated with hepatic steatosis and fibrosis in children with NAFLD. These results therefore suggest that hepatocyte apoptosis and macrophage activation are possible mechanisms by which NAFLD develops in the context of OSA in obese children.

Growth

Nachalon et al. studied the growth of 16 toddlers (6–36 months) pre and post-AT [56]. There was a significant increase in BMI Z score and caloric intake with a corresponding decrease in hsCRP levels following surgery. Subsequent multivariate analysis, demonstrated the improvement in somatic growth correlated with the improvement in systemic inflammation, rather than with changes in caloric intake. However, the numbers of subjects recruited were small, and this association was just seen in the boys, indicating the need for more research to validate and elucidate possible mechanisms. The findings are supported by the statistical modeling of anthropomorphic data from the CHAT study. The findings from this randomized trial showed that the BMI *z* score increased more in the children who underwent AT, than in those who were randomly assigned to watchful waiting, even among the children who were already overweight at baseline [57]. The long-term effects of POSA on weight and adipose tissue mass dynamics are still unknown, but these findings highlight the importance of weight monitoring, nutritional counseling, and encouragement of physical activity after AT for POSA.

Long-Term Morbidity

Recent Australian publications have examined the long-term outcomes 3 years after the resolution of POSA in pre-school children. Autonomic function was studied using power spectral analysis of heart rate variability and measurement of urinary catecholamines [58]. Overall, the resolution of POSA resulted in the normalization of previously elevated heart rate variability to levels that were similar to controls. In contrast, the children with residual POSA exhibited increased high-frequency HRV, suggesting a significant increase in their respiratory effort, though interestingly, this was also the case even in children with primary snoring. There was also a positive correlation between urinary catecholamines and low frequency power in children with unresolved POSA suggesting increased sympathetic activity in children with increasing severity of the OSA.

When these investigators examined behavioral and cognitive outcomes, behavioral functioning remained significantly worse in children who had been diagnosed with POSA compared with controls, and cognitive functioning decreased between baseline and follow-up, regardless of whether resolution of the POSA had occurred [59]. Indeed, these findings were in agreement with the Horne's laboratory earlier study examining the long-term outcomes of treatment in older school-aged children. This prior study also showed there were improvements in performance IQ, but not verbal IQ or academic measures, and no improvements in behavioral functioning [60]. These findings challenge the current paradigm generated from shorter-term follow-up studies which have generally shown favorable outcomes following treatment of POSA

[61•, 62]. The authors postulate that these less propitious findings may be the consequence of an acute "placebo-like" treatment effect, whereby parental perceptions of behavior are a reflection of improved sleep, or that the expectation of improvement with AT may have biased their responses when completing behavioral questionnaires in the short-term, but such "placebo effect" decreases when assessments are conducted at later time frames. Alternatively, it may be that an insult to a developing brain during a vulnerable period may result in long-term sequelae, and certain children may be genetically more at risk. Certainly, genetic factors such as NADPH oxidase p22 subunit gene polymorphisms, IGF-1 and apolipoprotein E allelic variants have previously been shown to account for discrepancies in the neurocognitive performance in children with similar severities of OSA [63–65].

Diagnosis of OSA

The gold standard for diagnosis of POSA is currently an in-lab polysomnogram (PSG). While PSGs provide an objective measure of sleep architecture and disturbances in respiratory parameters, they are expensive in terms of time, labor and resources and are not easily available in many countries. This has prompted efforts towards validation and implementation of home sleep apnea testing in the past few years. This move has been driven not only by financial and institutional concerns, but also because of the potential to measure a more typical night's sleep as the child is sleeping at home in their own bed. Two large studies have demonstrated that it is possible to perform high quality home PSGs in children ≥5 years old in the research setting [66, 67]. However, of most interest is in-home respiratory polygraphy testing as these tests are less time consuming to set up and score. Alonso-Alvarez et al. compared home RP with in-lab PSG in 50 children clinically suspected to have OSA [68••]. Trained nursing staff went to the child's home to set up the study and initiate the recordings. All the home RP studies were successful and the area under the curve was consistently >90 % when various PSG cut-off values OAHI ≥1, 3 and 5/h TST were used, i.e., there was good agreement with in-lab PSGs. These results suggest the validity of home RP for the diagnosis of POSA in children with a high pre-test probability of having OSA. However, more research is required with regards to how to further optimize the sensitivity and specificity of home sleep-apnea testing in children with mild POSA.

Treatment of OSA

Adenotonsillectomy

The latest Cochrane systematic review to examine the evidence comparing AT versus non-surgical management of pediatric OSA found only three prospective trials that met the inclusion criteria [69]. The CHAT study data provided the highest quality evidence and was the main basis for the recommendation that in healthy children with mild/moderate POSA, AT was of benefit, but physicians and parents should carefully weigh the benefits and risks of AT against watchful waiting in these children as the condition may recover spontaneously over time. The Cochrane review also reported that the evidence for the benefit of AT in children with clinical symptoms of POSA but with negative PSG recordings, is of low quality and is therefore inconclusive [70]. The third study was a prospective study comparing AT versus CPAP in 80 syndromic children with either trisomy 21 or mucopolysaccharidoses with mild to moderate OSA [71]. These children had a baseline PSG, Epworth Sleepiness Score and OSA-18 QOL questionnaire which were repeated at follow-up a year later. Outcomes in the two groups were similar although CPAP gave immediate sustained improvement while AT showed a more gradual progressive improvement in symptoms. The failure rate was 8.1 % in the AT group, due to multilevel obstruction/hypotonia and compensatory hypertrophy of the lingual tonsils. 13.8 % failed treatment in the CPAP group due to poor compliance or grade 4 adenotonsillar hypertrophy. Although the authors conclude that AT can be the first line treatment even in carefully selected syndromic children, we would temper such conclusion by suggesting that AT can be of benefit in these children, but each case needs to be assessed on an individual basis.

A further recent meta-analysis which also included retrospective studies found that AT results in improvements in a variety of sleep parameters such as sleep efficiency, increase in slow wave and REM sleep [72]. Outcomes in non-obese children were better than those for obese children. Post-operative residual OSA was apparent in approximately half of the children, especially those with severe disease and obesity.

When examining the risk-benefit ratio, recent studies have looked at the safety of AT. AT is generally considered as a safe procedure. However, like all surgical procedures there can be complications. The most common complications are respiratory compromise and secondary hemorrhage [73]. Children with POSA have an increased risk of respiratory complications after AT than children without (odds ratio 4.9). However, they appear less likely to have post-operative bleeding compared with children without POSA (odds ratio 0.41). One possible explanation is the other main indication for AT is recurrent tonsillitis and this may be a risk factor for secondary hemorrhage rather than POSA being a protective factor. Of note, from the CHAT study, none of the PSG or demographic parameters predicted post-operative complications [74].

Some researchers have suggested that drug induced sleep endoscopy (DISE) should be routinely performed prior to AT in all children so that multilevel obstruction can be identified. Boudewyns et al. have routinely performed this procedure in children with POSA in whom upper airway surgery was being considered [75]. Their experience in 37 children showed that adenotonsillar obstruction of the upper airway was apparent in 33 cases, with 28 subsequently treated with AT, 3 with adenoidectomy and 2 with tonsillectomy. The remaining 4 children received non- surgical treatment (CPAP/orthodontics). In those who underwent surgery, the success rate was 91 %, leading the authors to advocate DISE as a routine examination in all children with POSA prior to upper airway surgery. This is a controversial proposal as it would have significant implications on resources and workloads. DISE has until now been mainly used in the assessment of children who have residual OSA post-AT, or in complicated OSA such as that seen in children with craniofacial abnormalities, cerebral palsy, trisomy 21 etc. Indeed, a recent meta-analysis concluded that DISE is probably only of benefit in a minority of children, and should thus be limited to those whole clinical evaluation does not reveal tonsillar/adenoidal hypertrophy or when there is residual OSA post-AT [76].

Medical Therapy

One of the alternatives to AT for treatment of mild OSA is medical therapy, namely montelukast and intranasal steroids. A recent large retrospective review of 752 children with mild POSA who received nasal steroids and montelukast showed an overall success rate of 80.5 % [77•]. Follow-up polysomnography in a subset of 445 patients showed normalization of sleep findings in 62 %. Older children aged >7 years and obese children were less likely to respond favorably.

Guidelines

A final note should be made to the latest American and European guidelines. In 2012, the American Academy of Pediatrics (AAP) updated their guidelines on the diagnosis and management of children with POSA [1]. These guidelines focused on uncomplicated OSA, i.e., POSA associated with adenotonsillar hypertrophy or obesity in otherwise healthy children. Reviewing the data from articles published between 1999–2010, their main recommendations included:

- PSG should be performed in children who snore and have signs and symptoms of POSA.
- Should PSG not be available, alternative diagnostic tests or referral to a specialist for more extensive evaluation should be considered.
- Adenotonsillectomy is the treatment of choice in patients with POSA associated with adenotonsillar hypertrophy. Post operatively, high-risk patients should be monitored as inpatients.
- Patients should be reevaluated postoperatively to determine whether there is residual OSA and if further treatment is required. Objective testing should be performed in patients who are high-risk or have persistent symptoms/signs of POSA after therapy.
- If adenotonsillectomy is not performed, or if there is residual OSA, CPAP is recommended.
- Intranasal corticosteroids should be considered in children with mild POSA in whom adenotonsillectomy is contraindicated or for mild residual OSA post adenotonsillectomy.
- Weight loss should be recommended in patients who are overweight/obese.

The European Respiratory Society has more recently published guidelines on the diagnosis and management of obstructive sleep-disordered breathing in 2–18-year-old children [78]. Although the recommendations inevitably overlap with the AAP document, the ERS Guidelines aim to be different by not only discussing uncomplicated POSA, but also by including recommendations regarding conditions such as craniofacial anomalies and neuromuscular disorders. Consideration of the variability in diagnostic facilities available in different European countries was also taken into account. Based on articles published until 2014, a stepwise approach to the diagnosis and management of obstructive sleep-disordered breathing was suggested which has been summarized in Table 1. A subsequent document regarding infants is currently in the pipeline.

Future Research

An official American Thoracic Society statement on the importance of healthy sleep was released this year. It recommends the need for better education and raising awareness of both physicians and the general public with regards to the importance of early identification of high-risk OSA groups because of the significant public health implications of untreated OSA [79]. The research priorities it highlights include determining the molecular basis for OSA and using knowledge of these pathways to develop effective therapies, as well as identifying the etiological role of OSA in the development of comorbidities and determining the impact of OSA treatment on these comorbidities.

Another important area of research is in identifying biomarkers for OSA-associated morbidities. PSGs are poorly predictive of these: not every child fulfilling PSG criteria for POSA manifests end-organ morbidity, and conversely, some

Table 1 Stepwise approach to the diagnosis and management of OSA in children aged 2–18 years (adapted from ERS guidelines)

Step 1—Identification of a child at risk of OSA
Enquire about symptoms such as snoring, mouth breathing, witnessed apneas, restless sleep
Examination findings to look out for include tonsillar hypertrophy, obesity, mandibular hypoplasia, midface deficiency, evidence of conditions commonly associated with OSA including neuromuscular conditions, trisomy 21, Prader-Willi syndrome, etc.
Objective findings from investigations such as lateral neck radiograph (e.g., adenoid: nasopharyngeal ratio), flexible nasoendoscopy, cephalometry, upper airway MRI or CT.
Risk factors such as prematurity or family history of OSA
Step 2—Identification of morbidity and conditions coexisting with OSA
Cardiovascular morbidity, e.g., raised blood pressure, pulmonary hypertension
Neurocognitive morbidity, e.g., academic impairment, excessive daytime sleepiness, inattention, hyperactivity, behavioral problems
Failure to thrive
Nocturnal enuresis
Conditions coexisting with OSA include oromotor dysfunction, asthma, metabolic syndrome, recurrent otitis media
Step 3—Recognition of factors predicting persistence of OSA
AHI > 5/h
Male gender
Obesity
Afro-Caribbean ethnicity
Craniofacial features such as narrow mandible
Step 4—Objective diagnosis and assessment of disease severity
PSG or polygraphy
If not available, alternatives include ambulatory PSG, nocturnal oximetry, sleep clinical record or pediatric sleep questionnaire
Step 5—Indications for treatment
AHI > 5/h
If 1 > AHI > 5/h, treatment may be beneficial if any of the morbidities mentioned in Step 2 are present
Treatment of OSA should be a priority in conditions such as craniofacial syndromes, trisomy 21, neuromuscular conditions, Prader-Willi syndrome, mucopolysaccharidoses, achondroplasia, chiari malformation
Step 6—Treatment interventions should be implemented in a stepwise manner addressing all abnormalities that predispose to OSA
Weight loss in children who are overweight/obese
Medical therapy (nasal steroids/montelukast)
Adenotonsillectomy
Rapid maxillary expansion/orthodontic appliances
CPAP or NIV
Tracheostomy
Step 7—Recognition and management of residual OSA
Re-evaluation following intervention (symptoms, morbidities, PSG or if not available, polygraphy/oximetry and capnography).
If OSA symptoms persist or at risk of residual OSA, PSG ≥ 6 weeks after adenotonsillectomy or ≥12 weeks after medical therapy
PSG 12 months after rapid maxillary expansion, 6 months with an oral appliance
PSG for initial titration of CPAP/NIV, then at least yearly
Monitoring with PSG to guide tracheostomy decannulation
When residual OSA is demonstrated, airway re-evaluation by drug induced sleep endoscopy, nasopharyngoscopy, or MRI may help identify additional upper airway abnormalities

children with primary snoring already display sequelae despite a normal sleep study. Proteomic approaches in conjunction with bioinformatic approaches have revealed that POSA is associated with specific and consistent alterations in certain urinary proteins [80]. Increased levels of urinary catecholamines epinephrine and nor-epinephrine have been identified and overnight increases in GABA, decreases in taurine and β-phenylethylamine (PEA) appear to differentiate children with POSA with neurocognitive deficits from those without [81]. There is also emerging data on exosomal miRNAs as potential biomarkers of cardiovascular risk in children with POSA [82]. High sensitivity CRP, a test that is already clinically widely available in clinical practice, has also been recently demonstrated to be a potential biomarker for residual OSA [12]. As we advance into the era of personalized medicine, coordinated combinatorial approaches will need to be developed so that the diagnosis and treatment can be tailored to the individual patient.

Conclusions

Overall, the progress in our understanding of pediatric OSA has been remarkable in the past few years. As can be readily seen from this review, the unique features of the pediatric population are increasingly being recognized and investigated, and pediatric sleep research groups are at the forefront of biomarker discovery, and the development of personalized

medicine. The fact that many worthy papers could not be included here due to limitations of space, further attests to the breadth and quality of ongoing research and bodes well for the future of our field and the welfare of children.

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Compliance with Ethical Standards

Conflict of Interest Hui-Leng Tan, David Gozal, and Leila Kheirandish-Gozal declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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