The Journal of Laryngology & Otology (2018), ***132***, *284–292*.

doi:10.1017/S0022215118000208

REVIEW ARTICLE

Paediatric obstructive sleep apnoea: can our identification of surgical candidates be evidence-based?

L PABLA, J DUFFIN, L FLOOD, K BLACKMORE

ENT Department, James Cook University Hospital, Middlesbrough, UK

Abstract

Background: Paediatric obstructive sleep apnoea is a common clinical condition managed by most ENT clinicians. However, despite the plethora of publications on the subject, there is wide variability, in the literature and in practice, on key aspects such as diagnostic criteria, the impact of co-morbidities and the indications for surgical correction.

Methods: A systematic review is presented, addressing four key questions from the available literature: (1) what is the evidence base for any definition of paediatric obstructive sleep apnoea?; (2) does it cause serious systemic illness?; (3) what co-morbidities influence the severity of paediatric obstructive sleep apnoea?; and (4) is there a medical answer?

Results and conclusion: There is a considerable lack of evidence regarding most of these fundamental questions. Notably, screening measures show low specificity and can be insensitive to mild obstructive sleep apnoea. There is a surprising lack of clarity in the definition (let alone estimate of severity) of sleep-disordered breathing, relying on what may be arbitrary test thresholds. Areas of potential research might include investigation of the mechanisms through which obstructive sleep apnoea causes co-morbidities, whether neurocognitive, behavioural, metabolic or cardiovascular, and the role of non-surgical management.

Key words: Child; Tonsillectomy; Sleep Apnea, Obstructive; Comorbidity; Polysomnography

Introduction

Obstructive sleep apnoea (OSA) is a disorder of breathing during sleep, characterised by prolonged partial upper airway obstruction and/or intermittent complete obstruction (obstructive apnoea), which disrupts normal ventilation during sleep and normal sleep patterns.[1] Diagnosis is based on history, examination, apnoea/hypopnoea index score and other respiratory disturbances on polysomnography. Primary snoring is defined as snoring without obstructive apnoea, frequent arousals from sleep or gas exchange abnormalities.

The challenge is to differentiate primary snoring from OSA in a cost-effective, timely and reliable manner. The role of co-morbidities in determining the severity of OSA, the impact on health and the place of medical treatment is uncertain. Despite the increasing abundance of publications on paediatric OSA, there is a limited knowledge base to guide investigation and management.[2] This review systematically assesses the evidence base for diagnosis of paediatric OSA, its clinical significance and non-surgical options for management.

Materials and methods

This review adheres to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols ('PRISMA-P'), 2015. Papers were assessed using the National Institute for Health and Care Excellence quality assessment tool, which allows some analysis of case reports and series (lower level evidence).

We sought high-quality prospective clinical studies, reviews or laboratory work relevant to the definition, diagnosis, classification and non-surgical management of paediatric OSA. A search of Medline, Embase and Cochrane Library databases, from inception up to March 2017, was conducted, using the following keywords and combinations thereof: 'obstructive sleep apnoea', 'obstructive sleep apnea', 'paediatric', 'pediatric', and 'controlled trials/systematic review/evidence base'.

Abstracts, identified from a review of article titles, were evaluated for inclusion by two authors (LP and KB) working independently, with consensus if opinions differed. Papers were chosen if the abstracts

Accepted for publication 16 November 2017 First published online 14 February 2018

suggested systematic reviews or meta-analyses, prospective controlled studies, or original basic science findings from laboratory studies. Audits and larger case series or cohort studies, especially those offering any comparative study between groups, or before and after intervention, provided a lower level of evidence. Papers suggesting algorithms and consensus views for treatment, together with case reports suggesting complications and the earliest reports of the condition were also included.

Abstracts were excluded if they suggested isolated case reports or small and uncontrolled series that presented no new insight. No language restrictions were applied.

Results

We selected 55 papers that met the criteria for this review, all of which are referred to in the text: 23 systematic reviews;[1–23] 8 randomised controlled trials;[24–31] 5 non-randomised controlled or comparative studies;[32–36] 14 case series or cohort studies;[37–50] 5 surveys, consensus documents or questionnaires;[51–55] 0 historical articles; and 0 case reports.

Discussion

Question one

How is paediatric OSA defined? What is the evidence base for any threshold in polysomnography, apnoea/hypopnoea index or pulse oximetry?

Diagnostic methods that have been scientifically evaluated for predicting and assessing the severity of OSA in children include: history and physical examination, abbreviated polysomnography (pulse oximetry), and full polysomnography.

The American Academy of Pediatrics recommends screening all snoring children for OSA, but offers no recommended clinical screening protocol.[1] Screening is typically based on the parents' report of habitual snoring, apnoeic episodes, restless sleep and behavioural problems, combined with the physician's assessment of the clinical tonsil size. Polysomnography is considered the 'gold standard' investigation for children with suspected OSA, but is not routine because of a perceived lack of validated normative data, and financial and time considerations. Indeed, the UK multidisciplinary working party and American Academy of Otolaryngology – Head and Neck Surgery Foundation suggest reserving polysomnography for higher-risk patients.[52,53] A recent survey of UK practice found that only 25 per cent of respondents performed polysomnography prior to surgery, with 84 per cent electing for pre-operative pulse oximetry instead.[55]

A recent, comprehensive systematic review of evidence on diagnostic tests for OSA assessed their diagnostic test accuracy, comparing them to polysomnography as the standard reference.[14] Abbreviated sleep-based polysomnography (pulse oximetry), anterior rhinomanometry and urinary biomarkers (in which sophisticated laboratory techniques identify specific protein clusters) showed the best diagnostic test accuracy for diagnosing OSA in children when compared to polysomnography. Of these, urinary biomarkers showed the highest diagnostic test accuracy. Although the latter are promising and non-invasive, there are no data on costing and the requirement of laboratory facilities for such investigation. This review noted low-quality studies, with small sample sizes and ill-defined OSA.

History and physical examination. This poorly predicts severity of OSA, but can differentiate primary snoring from OSA. Although a sleep history and physical examination is routine in screening, studies show a lack of sensitivity and specificity.[11] The history can be misleading, as loudness of snoring may not indicate nor correlate with the degree of OSA. Children with OSA are obstructed primarily during rapid eye movement sleep, predominantly in the early morning hours when unobserved by their parents.

A systematic review compared the diagnostic accuracy of routine clinical history and physical examination with full polysomnography.[3] Clinical evaluation alone tended to significantly over-diagnose OSA (with a high level of evidence). Objective testing such as full polysomnography should be favoured to increase diagnostic test accuracy.

A meta-analysis of the evidence on the diagnostic accuracy of individual or combined clinical symptoms and signs in predicting paediatric OSA also found unreliability.[12]

There is equally limited evidence that OSA can be identified based on tonsil size. A systematic review compared subjective clinical assessment of the tonsil size in non-obese, non-syndromic children with objective assessment of OSA severity using polysomnography, to guide clinical decision-making.[8] Twenty studies were identified, the majority of them case series. Eleven showed a correlation between tonsil size and objective OSA, whereas nine did not, with the latter studies generally showing a higher quality score. The association between subjective paediatric tonsil size and objective OSA severity proves weak and is a poor guide to management.

The Childhood Adenotonsillectomy Trial ('CHAT') is a recent large-scale, landmark study.[29] This multicentre, single-blinded randomised control trial was conducted to assess the neuropsychological and health outcomes in children randomised to receive either early adenotonsillectomy or watchful waiting with supportive care. Baseline measurements from the 453 children in this study revealed that 64 per cent had grade III and IV tonsils, although univariate analysis revealed no association with increased apnoea/hypopnoea index. Furthermore, information on demographics and questionnaire responses did not robustly discriminate OSA severity.[30]

https://doi.org/10.1017/S0022215118000208 Published online by Cambridge University Press

Abbreviated polysomnography. Abbreviated polysomnography, essentially pulse oximetry, is increasingly used as an alternative to full polysomnography for diagnosis and severity grading. Overnight oximetry, compared with full polysomnography, in otherwise healthy children, has a positive predictive value of 97 per cent and a negative predictive value of 47 per cent. This suggests that oximetry is a reliable screen that is useful when results are positive; however, negative results require full polysomnography for a definitive diagnosis.[1]

A systematic review of normal reference values for nocturnal pulse oximetry parameters in children without sleep-disordered breathing and no abnormalities predisposing them to sleep-disordered breathing was conducted.[18] It found sufficient reference data in healthy children to derive normative values for nocturnal oximetry parameters in children with sleep-disordered breathing aged over one year. These were: mean baseline saturation = 97 per cent (range, 95–98 per cent); number of desaturations below 90 per cent = 1 per hour; and clusters of desaturations below the 95 per cent centile = 2.

A cluster of desaturations consists of five or more drops in blood oxygen saturation level (more than 4 per cent) within 10–30 minutes. A nocturnal oximetry recording with a duration of 6 hours or more is considered positive, or diagnostic for OSA, if it demonstrates at least three clusters of desaturation events and at least three blood oxygen saturation level drops to less than 90 per cent.[38]

From this, the McGill oximetry scoring system was introduced as a means to describe the severity levels of nocturnal hypoxaemia.[41] Most studies use these criteria. However, Kaditis *et al*. reported inconsistencies and recommended standardisation of reporting criteria in future studies.[18] They proposed that children with symptoms consistent with OSA, no other medical problems and a McGill score of more than 1 be referred for adenotonsillectomy without undergoing polysomnography. Those with moderately severe or severely abnormal oximetry (McGill score of 3 or 4) should undergo adenotonsillectomy within two weeks. Furthermore, the review by Kaditis *et al*. included a three-phased study which showed that a McGill score of 4 is accompanied by a 20–24 per cent risk of re-intubation, unplanned intensive care unit admission or interventions to prevent airway compromise.[18]

The oxyhaemoglobin desaturation index is another parameter used in oximetry to assess blood oxygen saturation level abnormalities in OSA. Oxyhaemoglobin desaturation index is defined as the number of times per sleep hour that the oxygen saturation drops by 3 per cent (oxyhaemoglobin desaturation index of 3) or 4 per cent (oxyhaemoglobin desaturation index of 4). A normal oxyhaemoglobin desaturation index of 4 represents 2.2 episodes per hour in healthy children aged over one year. A systematic review suggested that an abnormal oxyhaemoglobin desaturation index of 4, with a cut-off value set low (i.e. more than 2 episodes per hour), can detect both children with mild and those with moderate-to-severe OSA, whereas the McGill criteria identifies moderate-to-severe OSA.[18]

Full polysomnography. Full polysomnography, the gold standard test for OSA, is the only diagnostic test that quantifies the ventilatory and sleep abnormalities associated with sleep-disordered breathing and which can be performed at any age. There may, however, be a different pattern of apnoea in children, for which polysomnography is less sensitive, compared with adults. Any single night's polysomnography represents a 'snapshot', and there could be variability night-to-night, requiring repeated testing. Moreover, sleep quality may be reduced by the very disturbances involved in the interventional nature of polysomnography, the 'first night effect'.[2,11] Children with severely abnormal sleep studies seem at increased risk for complications of OSA; however, formal studies correlating polysomnographic parameters with adverse outcomes in children with OSA are lacking.[1]

Studies show wide heterogeneity when diagnosing OSA on polysomnography. Varying diagnostic criteria result in a lack of uniformity regarding standard definitions and what level of apnoea/hypopnoea index is considered abnormal.[7] Generally, in children older than one year undergoing laboratory-attended polysomnography, an apnoea/hypopnoea index of more than 1.5 is considered statistically abnormal. However, the cut-off values that define clinically significant abnormalities, or level at which treatment is likely to alter outcome are yet to be determined. Criteria to determine sleep-disordered breathing in infancy are even less well reported, with none defining an abnormal apnoea/hypopnoea index in children less than one year of age.[48]

Outcome data are severely lacking in paediatric OSA. No study has linked diagnostic thresholds with untoward outcomes in OSA, particularly in the area of neurocognitive dysfunction.[48] If polysomnography is to be unequivocally considered the gold standard test for OSA and predict harmful outcomes, appropriate polysomnography thresholds must be defined, or methods of testing linked to neurocognitive outcomes be developed. In addition, emerging evidence shows that even simple snoring has neurocognitive effects (particularly attention deficit hyperactivity disorder and learning disorders), and findings of the 'best' diagnostic test available (polysomnography) could be classed as 'normal' in a snoring child who is at risk of a poor outcome.[3]

A systematic review and meta-analysis of the diagnostic accuracy of polysomnography found major heterogeneity in the definition of scoring events (i.e. in the definition of an apnoea and diagnosis of OSA).[16] For example, apnoea was defined as the absence of oronasal flow lasting at least 6 seconds, but five studies defined it as an interruption of oronasal flow for a

https://doi.org/10.1017/S0022215118000208 Published online by Cambridge University Press

period of time at least equal to two respiratory cycles (with no mention of an objective time frame). Greater heterogeneity was found for hypopnoea scoring – there was no consensus on the duration of the event or even the definition of hypopnoea. Most of the included studies defined hypopnoea as a decrease of at least 50 per cent in the amplitude of respiratory flow; however, one study defined it as a decrease in the amplitude of the baseline. The criteria for diagnosis of OSA ranged from an apnoea/hypopnoea index of more than 1 to more than 5 episodes per hour. Despite American Academy of Sleep Medicine guidelines, only three studies used an apnoea/hypopnoea index of more than 1 episode per hour to diagnose paediatric OSA (range, 1–5 episodes per hour).[16]

Summary points. Current screening tests show a relatively high sensitivity, but a low specificity. Most are better at detecting moderate-to-severe rather than mild OSA. Emerging evidence suggests that even mild forms of OSA (and possibly even primary snoring) carry associated morbidity. There are limited studies investigating the threshold at which the apnoea/hypopnoea index predicts morbidity such as of cardiac and neurocognitive disorders. The ability of screening tests, other than polysomnography, to predict postoperative complications after adenotonsillectomy is unclear.

Question two

Is paediatric OSA really a serious clinical concern?

It is widely accepted that a child with OSA is at risk of developing significant morbidity. This review examines the evidence base for that assumption.

The majority of studies concentrate on the neurobehavioural, cardiovascular and metabolic effects of OSA, but show low quality with small sample sizes.[4,7,46] High-level evidence comes from the randomised controlled Childhood Adenotonsillectomy Trial, in which the primary outcome was a neurobehavioural measure of attention and executive function.[29] Children underwent cognitive and behavioural testing (objective psychometric testing, Developmental Neuropsychological Assessment ('NEPSY'), and subjective caregiver and teacher ratings of behaviour) at baseline and seven months after randomisation to either an early adenotonsillectomy group or a watchful waiting with supportive care group. After a seven-month intervention period, children who underwent adenotonsillectomy did not have a significantly greater improvement in attention and executive function, as measured by the Developmental Neuropsychological Assessment, compared to the watchful waiting group. However, secondary outcome measures revealed that surgery resulted in significantly greater improvements in executive function and behaviour (based on performance in activities of daily living according to caregivers), based on subjective Behaviour Rating Inventory of Executive Function ('BRIEF') scores. Previous research favoured this Behaviour Rating Inventory of Executive Function scoring system, representing real-world settings, over the closely supervised Developmental Neuropsychological Assessment environment. This study excluded children younger than five years of age, in whom OSA is most common, and the findings may therefore be unrepresentative.

The combined physiological disturbances associated with OSA lead to an increased risk of end-organ morbidities in children, particularly cardiovascular problems, such as endothelial dysfunction, systemic hypertension, pulmonary hypertension and myocardial left ventricular dysfunction.[9]

A systematic review found autonomic dysfunction in children with varying degrees of OSA, and noted altered autonomic cardiac control, as shown by heart rate variability, in children with severe OSA and in preschool children with moderate-to-severe OSA.[47] Furthermore, children with sleep-disordered breathing of any severity suffered from higher blood pressure at any time of the day, with occasional elevation to clinical hypertension. Baroreflex impairment, an abnormal autonomic response to stimuli and increased catecholamine levels were demonstrated in both OSA and primary snoring patients. Additionally, OSA induces chronic low-grade inflammation, increasing serum C-reactive protein, a relationship independent of other risk factors.[13] This may accelerate endothelial dysfunction and atherogenesis, and cause cardiovascular disease.

A prospective interventional study investigated the effect of adenotonsillar hypertrophy, found in approximately 80 per cent of children with OSA, on cardiopulmonary function.[50] Of the 25 children aged 3–18 years, there were significant improvements in pulmonary flow acceleration time ($p = 0.01$), mean pulmonary artery pressure ($p = 0.02$) and tricuspid regurgitation following adenotonsillectomy. The small cohort and lack of inclusion data regarding pulse oximetry limit the value of the findings, especially when, as shown above, adenotonsillar hypertrophy cannot reliably predict the likelihood of OSA in children.

Obstructive sleep apnoea has also been shown to be a risk factor for developing obesity, as demonstrated in the Tucson Children's Assessment of Sleep Apnea Study, a longitudinal study following up children with persistent OSA at five years.[43] This showed metabolic consequences, with lipid homeostasis and systemic inflammation being influenced by OSA, and in the presence of obesity there was an effect on glycaemic control.[4] The evidence on whether OSA effects serum lipid levels is lacking, as studies have shown altered levels in OSA but no improvement on treatment of sleep-disordered breathing.[19] Insulin sensitivity in children is preserved in those with OSA, but when combined with obesity, OSA proves to be an independent risk factor for insulin sensitivity.

An effect on endocrine function by sleep-disordered breathing was found in a prospective study of 70

https://doi.org/10.1017/S0022215118000208 Published online by Cambridge University Press

children aged 2.4–10.5 years.[39] This showed that both OSA and primary snoring children had reduced peripheral insulin-like growth factor-binding protein 3 levels. Furthermore, after surgery (six months post-adenotonsillectomy), children showed improved growth, and a significant increase in insulin-like growth factor 1 and insulin-like growth factor-binding protein 3.

Summary points. There is high-level evidence that significant morbidity results from sleep-disordered breathing in children with a clear need for early treatment. Morbidity can be broadly divided into neurocognitive and behavioural effects, metabolic effects, and cardiovascular effects. There is still much to be learnt in terms of understanding the mechanisms through which morbidity occurs and how it is influenced by the spectrum of sleep-disordered breathing.

Question three

What co-morbidities influence paediatric OSA?

Obesity. The increased prevalence of overweight and obese children is recognised as a major public health problem. The Health Survey for England data from 2015 reported that 28.2 per cent of 2–15 year olds were overweight or obese.[54]

Unsurprisingly, this cohort of children shows a higher prevalence of OSA, with studies reporting rates of 19–61 per cent.[20] A study of tonsil and adenoid sizes in 206 obese children with OSA and 206 matched non-obese children with OSA showed that the mean adenotonsillar size was larger in non-obese children than in the obese, suggesting that obese children have less lymphoid tissue for the same degree of OSA.[34] However, a magnetic resonance imaging based study of 38 obese children found that those with OSA had significantly larger adenotonsillar tissue and retropharyngeal nodes, larger parapharyngeal fat pads, and increased abdominal fat than those without OSA.[35]

Cognitive testing on three groups of children – OSA alone (36 children), obesity and polysomnography-proven OSA (38 children), and a control group (58 children) – revealed higher intelligence quotient (IQ) scores in the control group, and statistically significant lower scores in total IQ and a subtest of IQ (Performance IQ) in the obese OSA group compared with both other groups.[36] The limitation of most such studies of this population is the absence of a group showing obesity without OSA.

The effect of treatment on this group also needs to be considered. A comprehensive systematic review assessed the evidence on treatment methods and outcomes.[20] Five papers investigated the effect of adenotonsillectomy on OSA in obese and non-obese children. Whilst all had small study populations, four of the five studies showed an apnoea/hypopnoea index decline in all patients undergoing surgery, with the obese children benefitting less. The persistence of polysomnography-proven OSA following surgery for the non-obese patients ranged from 15 to 37 per cent, whilst in the obese group it ranged from 33 to 76 per cent.

There is limited evidence that weight loss (either behaviourally or surgically) improves OSA significantly. Behavioural weight loss resulted in persistent OSA in 33–38 per cent, and surgical weight loss resulted in persistent symptoms in 10–18 per cent. However, none of the studies included evaluated the amount of weight loss required to achieve this improvement in OSA.

The final treatment modality assessed was that of positive pressure ventilation. Whilst this intervention was shown in all studies to improve OSA, the main limiting factor was adherence to treatment.

Overall, the evidence suggests that multi-modal treatment will be required for children with obesity-related OSA. Adenotonsillectomy would be a suitable first-line treatment with adjuvant behavioural weight loss.

Asthma. Research has suggested an increased prevalence of asthma associated with obesity and sleep-disordered breathing.[44]

The relationship is postulated to be bi-directional, with sleep-disordered breathing or OSA exacerbating asthma by altering oropharyngeal reflexes, increasing intrathoracic pressure and cholinergic tone, and promoting bronchospasm.[44] Asthma may exacerbate sleep-disordered breathing by disrupting sleep and increasing the frequency of apnoeas in snorers.[51] Poorly controlled asthma may accentuate the hypoxaemia of sleep-disordered breathing, and vice versa, causing upper and lower airway inflammation.

A systematic review was conducted of 17 studies to investigate this association.[15] The meta-analysis found sleep-disordered breathing in nearly twice as many children with asthma than in those without. However, the studies included used diverse classifications for the diagnosis of asthma and varied definitions for sleep-disordered breathing. Polysomnography was only undertaken in two studies, compromising any association with OSA. Most of the studies used questionnaires completed by parents or carers, with no objective testing. A prospective observational study examined the relationship between obesity, sleep-disordered breathing and asthma severity in children.[44] It found, from a population of 108 obese children, that 29.6 per cent were asthmatic. After adjustment for variables, children with sleep-disordered breathing had 3.62-fold increased odds of having severe asthma at 1-year follow up. There was no assessment of symptomatic improvement for asthma with treatment of sleep-disordered breathing. The study lacked polysomnography to diagnose the sleep-disordered breathing, and there was the potential risk that desaturations on oximetry were secondary to asthma as opposed to upper airway obstruction.

https://doi.org/10.1017/S0022215118000208 Published online by Cambridge University Press

The evidence base for the effect of treatment of sleep-disordered breathing or OSA on asthma is limited by the variability in the quality of the studies, and the multiple different study designs and criteria used. A systematic review concluded that there was a statistically significant improvement in the clinical markers of asthma severity following adenotonsillectomy.[21] However, from an initial pool of over 500 papers, only 4 were included in the analysis. Of those, two were case series, one a database review and one a cohort study. A subsequent systematic review included five studies (two were included in the aforementioned review) that assessed the impact of treatment.[22] They could find no studies that assessed the effect of asthma treatment on sleep-disordered breathing when including only those that looked at the effect of adenotonsillectomy on asthma. The paper again concluded that there was a significant improvement in asthma (fewer exacerbations and hospital visits, decreased medication use). The studies were mainly retrospective (three out of five), with variable diagnostic criteria for asthma and sleep-disordered breathing.

Although studies suggest a link between asthma and sleep-disordered breathing, the quality of the research is poor. A large prospective study, which uses objective testing to investigate this association, is required.

Craniofacial anomalies. The association of Down's syndrome and OSA has been widely reported. However, OSA should be considered in all children with craniofacial anomalies, particularly if syndromal. Patients with craniosynostosis, cleft lip or palate, and associated Pierre Robin sequence and Treacher Collins syndrome, have an increased risk of OSA, with a reported prevalence of 7–67 per cent.[17] However, these figures were not obtained from prospective trials.

Whilst adenotonsillectomy is the first-line treatment in otherwise healthy children with adenotonsillar hypertrophy and OSA, in this population with craniofacial anomalies, studies have found a poorer surgical response.[49] Nasopharyngeal airways, mandibular distraction, midface advancement, positive pressure ventilation and ultimately tracheostomy have all been advocated as alternative treatments, as such children often have multi-level airway obstruction.[5,42,45] Most of the publications are case reports, case series or retrospective reviews with small heterogeneous populations and a lack of objective data.

Summary points. The increasing prevalence of childhood obesity demands multimodality treatment for associated OSA, possibly including adenotonsillectomy with adjuvant behavioural weight loss. More objective testing is required to investigate and establish the link between asthma and OSA. Children with craniofacial anomalies are at increased risk of OSA, but prospective, well-controlled studies on incidence, diagnostic criteria and treatment effects are lacking.

Question four

Is there a medical answer?

The management of paediatric OSA has centred on adenotonsillectomy, but there is some evidence for non-surgical management of this condition (medication, orthodontic treatments, and the use of continuous positive airway pressure (CPAP) or bilevel positive airway pressure).

Medication – intranasal steroids. Any benefit of intranasal steroids in paediatric OSA, with its recognised high prevalence of allergic rhinitis, is thought to be due to a reduction in upper airway resistance at a nasal, adenoidal and/or tonsillar level.[37]

Three randomised controlled trials (RCTs) used intranasal steroids in the treatment arms, and all quoted an improvement in several of the measured outcomes.[24,26,31]

This included a triple-blinded, placebo-controlled, parallel group trial, comprising a total of 25 patients, aged 1–10 years, with varying severities of OSA on polysomnography.[24] After a six-week course of fluticasone, the treatment group (13 patients) had a statistically significant fall in apnoea/hypopnoea index, from 10.7 to 5.8 episodes per hour, compared with an increase from 10.9 to 13.1 episodes per hour in the placebo group. There were improvements in oxygen desaturation index ($p = 0.03$), respiratory arousal index ($p = 0.05$) and patient-reported symptom scores in the treatment arm, but there was no change in the oxygen saturation nadir. Following the study, 46 per cent of patients in the treatment arm went on to have adenotonsillectomy, compared with 75 per cent in the control arm. However, the findings are based on a small sample size, and the long-term benefit is uncertain as the follow-up polysomnography was undertaken immediately after treatment.

A similar double-blinded crossover study of 62 patients reported that a 6-week course of intranasal budesonide significantly improved several polysomnography parameters (apnoea/hypopnoea index, oxygen saturation nadir, respiratory arousal index and other aspects of sleep macro-architecture) 8 weeks following treatment cessation.[26] The validity of the results, however, is affected by: an imbalance of the apnoea/hypopnoea index between the study groups at baseline, a large dropout rate in the placebo group following the first arm and the possibility of a carry-over effect that was not tested for.

The most recent RCT studied 62 older children (aged 11–18 years) with polysomnography-proven mild OSA, in which the treatment arm received 4 months of mometasone.[31] Fifty children completed the study. There was a statistically significant improvement in the apnoea/hypopnoea index and oxyhaemoglobin desaturation index in the treatment arm, based on repeat polysomnography performed at the conclusion.

Whilst all the studies showed an improvement in several of the outcome parameters, they all comprised

https://doi.org/10.1017/S0022215118000208 Published online by Cambridge University Press

small population groups and none had any long-term follow-up results. Each study used different treatment timescales, and different drugs and dosages. None of the studies looked at the effect of different dosages for the same duration or indeed for longer follow-up periods.

A Cochrane review of anti-inflammatory medications for OSA in children concluded that there may be a short-term benefit in terms of the apnoea/hypopnoea index for mild-to-moderate OSA using nasal steroids, but it recommended further RCTs.[10] It suggested these should use sleep studies and generally accepted evaluation criteria. The 'avoidance of surgery' was also suggested as an outcome measure, with longer-term assurance of sustained benefit.

The high levels of cysteinyl leukotrienes and increased expression of their receptors in the upper airway tissue of paediatric patients with sleep-disordered breathing led to the hypothesis that leukotriene modifier therapy, such as montelukast, may be of benefit in this population.[32]

Kheirandish *et al*. undertook a small study of 28 patients with residual mild sleep-disordered breathing following adenotonsillectomy.[33] Fourteen were assigned to treatment with a 16-week course of montelukast and budesonide, and 14 were in a control group. A repeat polysomnography performed at the end of the trial revealed a significant improvement in apnoea/hypopnoea index, oxygen saturations and respiratory arousal index, with no significant improvements in the control group. However, this study entailed non-randomised treatment allocation, and the combination of two drugs makes it impossible to separate their individual contribution. Again, the polysomnography was undertaken immediately following the intervention period, with no indication of the long-term benefit.

Goldbart and colleagues' randomised, double-blind study compared a 12-week course of montelukast with placebo (23 in each study arm).[27] The treatment arm had a statistically significant improvement in polysomnography findings in terms of the obstructive apnoea index and an improvement in sleep symptoms. There was a significant decrease in adenoid size in the treatment group on lateral X-ray, suggesting that the improvements in sleep-disordered breathing may be due to adenoidal rather than tonsil reduction, which should be considered if using this treatment in children with tonsillar hypertrophy.

Orthodontic interventions. Craniofacial anatomy is influenced by genetic and environmental factors. Upper airway obstruction with resultant mouth breathing can induce craniofacial anomalies. In patients with sleep-disordered breathing, these anomalies may improve or normalise with treatment by adenotonsillectomy.[6] Orthodontic treatment may also improve the craniofacial anomaly by increasing the size of the oropharyngeal airway.

Huynh *et al*. conducted a systematic review of orthodontic treatments for OSA in children, investigating the effect of mandibular advancement devices and rapid maxillary expansion.[23] Eight studies were included in the review. Mandibular advancement aims to improve retrognathia by altering mandibular growth, with more forward positioning of the mandible and consequently less collapsibility of the airway. Huynh and colleagues' review identified two studies using this treatment that showed improvements in apnoea/hypopnoea index on polysomnography following six months of using the device. There was a lack of comparable outcomes to allow cumulative analysis. Clinical heterogeneity and conclusions made without data evidence compromise any recommendations.

Rapid maxillary expansion aims to decrease nasal resistance, allowing tongue repositioning to reduce upper airway obstruction. Five studies in the review reported a total of 88 treated patients. Each study showed a decrease in the apnoea/hypopnoea index following treatment, but, once again, the heterogeneity of data compromised statistical significance. The studies differed in terms of: the various methods for rapid maxillary expansion, the requirement for wearing the device, the intervention length and the outcome measures.

Whilst there may be some benefit of orthodontic treatment in a specific paediatric OSA population, the literature is limited and the findings are inconclusive.

Positive airway pressure. The use of positive airway pressure in children with OSA is usually confined to those inappropriate for surgery or with residual symptoms following it. The former include children with craniofacial abnormalities, obesity, Down's syndrome or upper airway muscle weakness (e.g. cerebral palsy).[40]

Studies have shown the effectiveness of this treatment for OSA. However, it is not curative and will often require long-term use. Marcus *et al*. conducted a double-blind randomised multicentre study comparing bilevel positive airway pressure with CPAP in 29 children with polysomnography-proven OSA whose surgical treatment had failed or who were not considered surgical candidates.[25] Whilst both treatment arms showed a significant improvement in apnoea/hypopnoea index and oxygen saturation on polysomnography, after six months of treatment there was a drop out of approximately one-third of patients.

Compliance with positive airway pressure in the paediatric population is the challenge, and this requires motivated carers and behavioural techniques.[28]

Summary points. Three blinded RCTs showed improvement in several outcome measures with the use of intranasal steroids in children with OSA. However, the sample sizes were small and the studies lacked long-term follow up. Orthodontic treatments benefit a specific subset of children with OSA, namely those with

https://doi.org/10.1017/S0022215118000208 Published online by Cambridge University Press

craniofacial anomalies, but the evidence is limited. Continuous positive airway pressure and bilevel positive airway pressure may be useful for residual symptoms or those patients unable to undergo adenotonsillectomy. The limiting factor for its effectiveness is treatment compliance.

Conclusion

Much has been researched and discussed on the topic of paediatric OSA, including its definition, consequences and associations with other co-morbidities. Despite this, there remains wide variation in the investigations used to diagnose OSA, making it difficult to develop a reliable, robust knowledge base upon which to direct treatment decisions. In order to produce meaningful data, studies need to clarify fundamentals such as the definition of OSA and grading of severity to ensure uniformity in reporting. It will then be possible to produce and learn from high-quality studies, with meaningful data, in order to understand the morbidity of OSA and the long-term effects of treatment. This review has highlighted such gaps in our current knowledge base, and found areas for research development to drive the ambition of high-quality paediatric OSA guidelines applicable to clinicians managing this condition.

References

1 Marcus CL, Chapman D, Ward SD, McColley SA, Herrerias CT, Stillwell PC *et al*. Clinical practice guideline: diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics* 2002;**109**:704–12
2 Venekamp RP, Chandrasekharan D, Abel F, Blackshaw H, Kreis IA, Evans HE *et al*. Research into childhood obstructive sleep-disordered breathing: a systematic review. *Chest* 2017;**152**:51–7
3 Brietzke SE, Katz ES, Roberson DW. Can history and physical examination reliably diagnose pediatric obstructive sleep apnea/hypopnea syndrome? A systematic review of the literature. *Otolaryngol Head Neck Surg* 2004;**131**:827–32
4 Goldbart AD, Tal A. Inflammation and sleep disordered breathing in children: a state-of-the-art review. *Pediatr Pulmonol* 2008;**43**:1151–60
5 Ow AT, Cheung LK. Meta-analysis of mandibular distraction osteogenesis: clinical applications and functional outcomes. *Plast Reconstr Surg* 2008;**121**:54–69e
6 Praud JP, Dorion D. Obstructive sleep disordered breathing in children: beyond adenotonsillectomy. *Pediatr Pulmonol* 2008;**43**:837–43
7 Owens JA. Neurocognitive and behavioral impact of sleep disordered breathing in children. *Pediatr Pulmonol* 2009;**44**:417–22
8 Nolan J, Brietzke SE. Systematic review of pediatric tonsil size and polysomnogram-measured obstructive sleep apnea severity. *Otolaryngol Head Neck Surg* 2011;**144**:844–50
9 Bhattacharjee R, Kim J, Kheirandish-Gozal L, Gozal D. Obesity and obstructive sleep apnea syndrome in children: a tale of inflammatory cascades. *Pediatr Pulmonol* 2011;**46**:313–23
10 Kuhle S, Urschitz MS. Anti-inflammatory medications for obstructive sleep apnea in children. *Cochrane Database Syst Rev* 2011;(1):CD007074
11 Church GD. The role of polysomnography in diagnosing and treating obstructive sleep apnea in pediatric patients. *Curr Probl Pediatr Adolesc Health Care* 2012;**42**:2–25
12 Certal V, Catumbela E, Winck JC, Azevedo I, Teixeira-Pinto A, Costa-Pereira A. Clinical assessment of pediatric obstructive sleep apnea: a systematic review and meta-analysis. *Laryngoscope* 2012;**122**:2105–14
13 Gozal D, Kheirandish-Gozal L, Bhattacharjee R, Kim J. C-reactive protein and obstructive sleep apnea syndrome in children. *Front Biosc* (*Elite Ed*) 2012;**4**:2410–22
14 Brockmann PE, Schaefer C, Poets A, Poets CF, Urschitz MS. Diagnosis of obstructive sleep apnea in children: a systematic review. *Sleep Med Rev* 2013;**17**:331–40
15 Brockmann PE, Bertrand P, Castro-Rodriguez JA. Influence of asthma on sleep disordered breathing in children: a systematic review. *Sleep Med Rev* 2014;**18**:393–7
16 Certal V, Camacho M, Winck JC, Capasso R, Azevedo I, Costa-Pereira A. Unattended sleep studies in pediatric OSA: a systematic review and meta-analysis. *Laryngoscope* 2015;**125**:255–62
17 Caron CJ, Pluijmers BI, Joosten KF, Mathijssen IM, van der Schroeff MP, Dunaway DJ *et al*. Obstructive sleep apnoea in craniofacial microsomia: a systematic review. *Int J Oral Maxillofac Surg* 2015;**44**:592–8
18 Kaditis A, Kheirandish-Gozal L, Gozal D. Pediatric OSAS: oximetry can provide answers when polysomnography is not available. *Sleep Med Rev* 2016;**27**:96–105
19 Gileles-Hillel A, Kheirandish-Gozal L, Gozal D. Biological plausibility linking sleep apnoea and metabolic dysfunction. *Nat Rev Endocrinol* 2016;**12**:290–8
20 Anderson IG, Holm JC, Homoe P. Obstructive sleep apnoea in obese children and adolescents, treatment methods and outcome of treatment - a systematic review. *Int J Pediatr Otorhinolaryngol* 2016;**87**:190–7
21 Kohli N, DeCarlo D, Goldstein NA, Silverman J. Asthma outcomes after adenotonsillectomy: a systematic review. *Int J Pediatr Otorhinolaryngol* 2016;**90**:107–12
22 Sanchez T, Castro-Rodriguez JA, Brockmann PE. Sleep-disordered breathing in children with asthma: a systematic review on the impact of treatment. *J Asthma Allergy* 2016;**9**:83–91
23 Huynh NT, Desplats E, Almeida FR. Orthodontics treatments for managing obstructive sleep apnea syndrome in children: a systematic review and meta-analysis. *Sleep Med Rev* 2016;**25**:84–94
24 Brouillette RT, Manoukian JJ, Ducharme M, Oudjbane K, Earle LG, Laden S *et al*. Efficacy of fluticasone nasal spray for pediatric obstructive sleep apnea. *J Pediatr* 2001;**138**:838–44
25 Marcus CL, Rosen G, Davidson Ward SL, Halbower AC, Sterni L, Lutz J *et al*. Adherence to and effectiveness of positive airway pressure therapy in children with obstructive sleep apnea. *Pediatrics* 2006;**117**:442–51
26 Kheirandish-Gozal L, Gozal D. Intranasal budesonide treatment for children with mild obstructive sleep apnea syndrome. *Pediatrics* 2008;**122**:149–55
27 Goldbart AD, Greenberg-Dotan S, Tal A. Montelukast for children with obstructive sleep apnea: a double-blind, placebo-controlled study. *Pediatrics* 2012;**130**:e575–80
28 Marcus CL, Beck SE, Traylor J, Cornaglia MA, Meltzer LJ, DiFeo N *et al*. Randomised, double-blind clinical trial of two different modes of positive airway pressure therapy on adherence and efficacy in children. *J Clin Sleep Med* 2012;**8**:37–42
29 Marcus CL, Moore RH, Rosen CL, Giordani B, Garetz SL, Taylor HG *et al*.; Childhood Adenotonsillectomy Trial (CHAT). A randomized trial of adenotonsillectomy for childhood sleep apnea. *N Engl J Med* 2013;**368**:2366–76
30 Mitchell RB, Garetz S, Moore RH, Rosen CL, Marcus CL, Katz ES *et al*. The use of clinical parameters to predict obstructive sleep apnea syndrome severity in children: the Childhood Adenotonsillectomy (CHAT) Study randomized clinical trial. *JAMA Otolaryngol Head Neck Surg* 2015;**141**:130–6
31 Chan CC, Au CT, Lam HS, Lee DL, Wing YK. Intranasal corticosteroids for mild childhood obstructive sleep apnea - a randomised, placebo-controlled study. *Sleep Med* 2015;**16**:358–63
32 Goldbart AD, Goldman JL, Li RC, Brittian KR, Tauman R, Gozal D. Differential expression of cysteinyl leukotriene receptors 1 and 2 in tonsils of children with obstructive sleep apnea syndrome or recurrent infection. *Chest* 2004;**126**:13–18
33 Kheirandish L, Goldbart AD, Gozal D. Intranasal steroids and oral leukotriene modifier therapy in residual sleep-disordered breathing after tonsillectomy and adenoidectomy in children. *Pediatrics* 2006;**117**:e61–6
34 Dayyat E, Kheirandish-Gozal L, Sans Capdervila O, Maarefeya MM, Gozal D. Obstructive sleep apnoea in children: relative contributions of body mass index and adenotonsillar hypertrophy. *Chest* 2009;**136**:137–44

https://doi.org/10.1017/S0022215118000208 Published online by Cambridge University Press

35 Arens R, Sin S, Nandalike K, Rieder J, Khan UI, Freeman K *et al*. Upper airway structure and body fat composition in obese children with obstructive sleep apnoea. *Am J Respir Crit Care Med* 2011;**186**:782–7
36 Vitelli O, Tabarrini A, Miano S, Rabasco J, Pietropaoli N, Forlani M *et al*. Impact of obesity on cognitive outcome in children with sleep-disordered breathing. *Sleep Med* 2015;**16**: 625–30
37 McColley SA, Carroll JK, Curtis S, Loughlin GM, Sampson HA. High prevalence of allergic sensitization in children with habitual snoring and obstructive sleep apnoea. *Chest* 1997; **111**:170–3
38 Brouillette RT, Morielli A, Leimanis A, Waters KA, Luciano R, Ducharme FM. Nocturnal pulse oximetry as an abbreviated testing modality for pediatric obstructive sleep apnea. *Pediatrics* 2000;**105**:405–12
39 Nieminen P, Lopponen T, Tolonen U, Lanning P, Knip M, Lopponen H. Growth and biochemical markers of growth in children with snoring and obstructive sleep apnea. *Pediatrics* 2002;**109**:e55
40 Massa F, Gonsalez S, Laverty A, Wallis C, Lane R. The use of nasal continuous positive airway pressure to treat obstructive sleep apnoea. *Arch Dis Child* 2002;**87**:438–43
41 Nixon GM, Kermack AS, Davis GM, Manoukian JJ, Brown KA, Brouillette RT. Planning adenotonsillectomy in children with obstructive sleep apnea: the role of overnight oximetry. *Pediatrics* 2004;**113**:e19–25
42 Ahmed J, Marucci D, Cochrane L, Heywood RL, Wyatt ME, Leighton SE. The role of the nasopharyngeal airway for obstructive sleep apnoea in syndromic craniosynostosis. *J Craniofac Surg* 2008;**19**:659–63
43 Budhiraja R, Quan SF. Outcomes from the Tucson Children's Assessment of Sleep Apnea Study (TuCASA). *Sleep Med Clin* 2009;**4**:9–18
44 Ross KR, Storfer-Isser A, Hart MA, Kibler AM, Rueschman M, Rosen CL *et al*. Sleep-disordered breathing is associated with asthma severity in children. *J Pediatr* 2012;**160**:736–42
45 Nout E, Bannicnk N, Koudstaal MJ, Veenland JF, Joosten KF, Poublon RM. Upper airway changes in syndromic craniosynostosis patients following midface or monobloc advancement: correlation between volume changes and respiratory outcome. *J Craniomaxillofac Surg* 2012;**40**:209–14
46 Tan E, Healey D, Schaughency E, Dawes P, Galland B. Neurobehavioural correlates in older children and adolescents with obesity and obstructive sleep apnoea. *J Paediatr Child Health* 2014;**50**:16–23
47 Nisbet LC, Yiallourou SR, Walter LM, Horne RS. Blood pressure regulation, autonomic control and sleep disordered breathing in children. *Sleep Med Rev* 2014;**18**:179–89
48 DeHaan KL, Seton C, Fitzgerald DA, Waters KA, MacLean JE. Polysomnography for the diagnosis of sleep disordered breathing in children under 2 years of age. *Pediatr Pulmonol* 2015; **50**:1346–53
49 Moraleda-Cibrian M, Edwards SP, Kasten SJ, Berger M, O'Brien LM. Obstructive sleep apnoea pretreatment and post-treatment in symptomatic children with congenital craniofacial malformations. *J Clin Sleep Med* 2015;**11**:37–43
50 Mahajan M, Thakur JS, Azad RK, Mohindroo NK, Negi PC. Cardiopulmonary functions and adenotonsillectomy: surgical indications need revision. *J Laryngol Otol* 2016;**130**:1120–4
51 Chng SY, Goh DY, Wang XS, Tan TN, Ong NB. Snoring and atopic disease: a strong association. *Pediatr Pulmonol* 2004; **38**:210–16
52 Robb PJ, Bew S, Kubba H, Murphy N, Primhak R, Rollin AM. Tonsillectomy and adenoidectomy in children with sleep related breathing disorders: consensus statement of a UK multidisciplinary working party. *Ann R Coll Surg Engl* 2009;**91**:371–3
53 Roland PS, Rosenfeld RM, Brooks LJ, Friedman NR, Jones J, Kim TW *et al*. Clinical practice guideline: polysomnography for sleep disordered breathing prior to tonsillectomy in children. *Otolaryngol Head Neck Surg* 2011;**145**(1 suppl):S1–15
54 Health Survey for England, 2015. In: http://www.content.digital.nhs.uk/catalogue/PUB22610/HSE2015-Child-obe.pdf [5 January 2018]
55 Sharma SD, Kanona H, Kumar G, Kotecha B. Latest trends in the assessment and management of paediatric snoring and sleep apnoea. *J Laryngol Otol* 2016;**130**:482–9

Address for correspondence:
Miss Lakhbinder Pabla,
ENT Department,
James Cook University Hospital,
Marton Road, Middlesbrough TS4 3BW, UK

E-mail: Lakh.pabla.bal@gmail.com

Miss L Pabla takes responsibility for the integrity of the content of the paper
Competing interests: None declared