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Childhood obstructive sleep apnoea: an update

有關兒童阻塞性睡眠呼吸暫停症研究的最新發展

Objective. To review literature on epidemiology, complications, diagnosis, and treatment of childhood obstructive sleep apnoea.
Data source. Literature search of MEDLINE up to July 2004 using the following key words: 'obstructive sleep apnoea syndrome', 'children', 'epidemiology', 'complications', 'treatment', and 'polysomnography'.
Study selection. Literature and data related to the aspects of childhood obstructive sleep apnoea.
Data extraction. Relevant information and data were reviewed by the authors.
Data synthesis. There is a paucity of normal data on childhood obstructive sleep apnoea. Varying definitions and diagnostic criteria have been used in different studies, making direct comparison difficult. However, a small-scale local study found that the prevalence and clinical features of this condition were similar to data published overseas. Increasing evidence suggests that childhood obstructive sleep apnoea is associated with cardiovascular morbidity and neurocognitive dysfunction. Overnight polysomnography has remained the gold standard for diagnosing obstructive sleep apnoea but the diagnostic criteria has not been standardised nor correlated with the long-term outcome. Surgical intervention has remained the treatment of choice, although alternative therapies are being evaluated.
Conclusion. Consensus on the various important aspects of childhood obstructive sleep apnoea is still limited, especially the definition, diagnosis, and long-term sequelae of this condition. Further advances can only be made with international collaborative research, using evidence-based definitions, standardised techniques, and polysomnographic criteria.

目標：回顧關於兒童阻塞性睡眠呼吸暫停症的文獻，包括流行病學、併發症、診斷與療法的探討。
資料來源：應用 MEDLINE 檢索系統，以 "obstructive sleep apnoea syndrome"(阻塞性睡眠呼吸暫停綜合徵)、"children"(兒童)、"epidemiology"(流行病學)、"complications"(併發症)、"treatment"(療法)，以及 "polysomnography" (多導睡眠監測)為關鍵詞，檢索截至 2004 年 7 月為止的相關文獻。
研究選擇：與兒童阻塞性睡眠呼吸暫停症有關的文獻和數據。
資料提取：由本文作者評述相關的資料和數據。
資料綜合：與兒童阻塞性睡眠呼吸暫停症有關的正規資料一向相當缺乏，研究所採用的定義和診斷標準各不相同，使結果難以直接比較。一項本地小規模研究發現，該症的普遍程度和臨床特徵與海外研究所得結果相似。越來越多證據顯示，兒童阻塞性睡眠呼吸暫停症跟心血管病和神經認知功能失調有關。目前，過夜多導睡眠監測仍然是診斷該症最有效的方法，但斷症的準則還未標準化，其長遠後果亦還未有確定的相關性。在評估其他各種療法後，手術治療仍是目前最為有效的一種療法。
結論：目前醫學界對兒童阻塞性睡眠呼吸暫停症的一些重要範疇還沒有達成一致看法，特別是對定義、診斷和長遠的後遺症，觀點不一。醫學界必須加強國際合作研究，採用以實證為基礎的定義、標準化的技術，以及多導睡眠監測的標準，才能在這方面的研究有所突破。

Key words:
Child;
Polysomnography;
Sleep apnea, obstructive

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Introduction

Obstructive sleep apnoea (OSA) has been increasingly recognised in children. Although the knowledge and understanding of paediatric OSA has expanded

exponentially over the past few years, diagnostic and mechanistic questions still remain. Most authors would concur that polysomnography (PSG) is the gold standard for the diagnosis of OSA and the treatment of choice is adenotonsillectomy, which has a high curative rate and relatively low morbidity. Recent evidence indicates that childhood OSA cannot be easily classified into simple clinical entities. Associated symptoms of OSA may vary and are frequently difficult to detect. The diagnosis of OSA in children is far from straightforward—for example, using PSG is a grossly simplified method to separate snoring children into specific categories. Close postoperative monitoring of all children with OSA cannot be overemphasised. The focus has been to prevent the postoperative airway and respiratory complications in this group of children. This article focuses on the new developments, controversies of this important condition, and results of local research.

Definition of obstructive sleep apnoea

Currently, no standard definition for childhood OSA is widely accepted. Knowing that childhood sleep disordered breathing (SDB) is a continuum with OSA on the severe end of this continuum, it seems reasonable to consider classic OSA, obstructive hypoventilation, and snoring with daytime symptoms as manifestations of the same underlying pathophysioloy, under the heading 'childhood obstructive SDB'.

Childhood OSA is a disorder of breathing during sleep characterised by prolonged increased upper airway resistance, partial upper airway obstruction, or complete obstruction that disrupts pulmonary ventilation and oxygenation. Night-time manifestations reducing the quality of sleep include combinations of snoring, increased respiratory effort, episodic hypoxaemia, carbon dioxide retention, choking during sleep, restlessness, sleeping with the neck hyper-extended, and frequent awakening. Daytime symptoms include excessive sleepiness, tiredness, fatigue, poor attention span, hyperactivity, poor school performance, aggressiveness, failure to thrive, and other subtle behavioural disturbances.[1]

The diagnosis of upper airway resistance syndrome (UARS) in children is, however, controversial.[2] In the Clinical Practice Guideline for Diagnosis and Management of Childhood Obstructive Sleep Apnea (2002) published by the American Academy of Pediatrics, it did not explicitly acknowledge the existence of UARS nor did it differentiate this condition from primary snoring.[3] In view of this controversy and lack of standard guidelines, this current review will not differentiate UARS from primary snoring and we will concentrate on OSA as our main topic of discussion.

Epidemiology

Snoring is the hallmark symptom of childhood OSA and its prevalence has been found to be greater than 15% among school children in recently published local studies.[4,5] Little is known about how snoring progresses in children as they grow up. Ali et al[6] looked at the natural progression of snoring in a cohort of children aged from 4 to 7 years and found that the overall prevalence of snoring had not changed (12.1% in 1989-90 versus 11.4% in 1992). More than half of the cohort aged between 4 and 5 years had habitual snoring, but no longer did so by 7 years old. Reports have shown that the majority of children with primary snoring do not progress to OSA.[7,8] The prevalence of snoring in adolescents and adults is higher than that reported for preadolescent children, suggesting that snoring increases with age.

Local data on the incidence of OSA are still limited in availability. In our previous local study involving obese children and randomly selected normal weight controls, the prevalence of OSA among the control group was between 2.3% and 4.5%.[4] The study, however, only recruited 44 normal children and may not be a true representation of the population of Hong Kong. Overseas studies have reported the estimates to be between 1% and 3%,[9-11] and in one series the prevalence rate was even 10.3% based on the diagnostic cut-off of the apnoea-hypopnoea index of more than 5 episodes per hour.[11] It is important to note that all these studies had methodological flaws because the conventional PSG used adult rather than paediatric polysomnographic diagnostic criteria, or a high-risk sample from the population was selected. A well-designed population-based cohort study with an adequate sample size is urgently required to determine the prevalence of OSA in our locality.

The most common cause for childhood OSA is adenotonsillar hypertrophy and the highest incidence is between the ages of 4 and 8 years. Obesity is another important factor for OSA because obese children are 10 times more likely to suffer from this condition than normal weight controls.[4] Other co-morbidities that could increase the risk for OSA are allergic rhinitis, neuromuscular disease, craniofacial anomalies, Down syndrome, and premature birth.[3,12]

Clinical features of obstructive sleep apnoea

Snoring is the most common night-time symptom of paediatric OSA. Children may exhibit continuous snoring interrupted by apnoeic pauses followed by arousals. The snoring sounds from OSA subjects are high-pitched and may be harsher than the classic 'nasal' snoring and some parents may not realise that their child is snoring because of noisy breathing during sleep. Besides, parents may not sleep in the same room with their child and may be unaware of the child's sleep breathing pattern. Hence, simple screening questions, for example, "Does your child snore?" may yield a false negative answer.

In children, OSA tends to occur mainly in rapid eye

movement (REM) sleep[13]; hence, snoring or pauses may be absent for long periods during the night. Rapid eye movement sleep accounts for around 25% of one's total sleep. Because OSA in children is most prominent during REM sleep, no apnoeas or features of OSA may be seen during the other 75% of one's sleep. Interestingly, surgical intervention considerably reduced the number of obstructive episodes in only the non-REM sleep. Other non-anatomical factors may be important in contributing towards obstructive apnoeas related to REM sleep. It is common for children with OSA to exhibit a pattern of partial upper airway obstruction with few or even no complete obstructive episodes.[14]

Children with OSA may have increased respiratory effort, which is manifested clinically as a paradoxical inward rib cage motion, and some parents may describe this as 'struggling' to breathe during sleep. It is important to note that paradoxical inward rib cage motion on its own is normal in children during REM sleep until the age of 3 years. Cyanosis is, however, rarely observed, even in severe cases of childhood OSA. In addition to the other symptoms mentioned, enuresis during night-time sleep has been frequently linked with childhood OSA, but subsequent studies including our own cohort study have not confirmed this association.[15,16]

A major difference between children and adults suffering from OSA is the relative rarity of daytime somnolence in the former. Previous studies using multiple sleep latency tests confirmed that most children with OSA do not have excessive daytime sleepiness (EDS).[4,17] Studies from the early 1980s showed that children with OSA may exhibit other daytime behaviour including social withdrawal, hyperactivity, aggressiveness, tiredness, and fatigue.[3] Daytime mouth breathing is a common finding in children with adenotonsillar hypertrophy and also in OSA.[3,15] Morning headache, as a symptom of childhood OSA, has also been reported by several authors, although one of the few controlled studies of childhood OSA did not confirm this association.[3] Accumulating evidence suggests that children with primary snoring suffer from similar daytime behaviour and cognitive dysfunction to that of SDB.[18] Also, children with classic OSA have been reported to have a clear association of SDB with poor school performance and other manifestations of impaired daytime cognitive function.[18]

Sequelae of obstructive sleep apnoea

Neurocognitive abnormalities

Despite the apparent relative absence of EDS in childhood OSA,[19] OSA and even snoring seem to be associated with considerable behavioural and learning difficulties, poor attention span, hyperactivity, and a below-average intelligent quotient.[20-26] The underlying mechanism causing the neurocognitive dysfunction is unclear, but it can be reversed following treatment.[23-26] Gozal et al[27] established that exposure to intermittent hypoxia during sleep cycle of adult rats is associated with extensive spatial learning deficits and increased neuronal apoptosis within the susceptible brain regions, such as the hippocampus and cortex. In a subsequent study by the same group, the up-regulation and activation of cyclooxygenase-2 was suggested to account for the hypoxia-induced spatial deficits as seen in the rats.[28] Additional investigation will be needed to determine whether the same mechanism applies to humans. Furthermore, there is current evidence to suggest that micro-arousals or subcortical arousals could also play a part in neurocognitive dysfunction seen in childhood OSA.[29] Patients did not seem to be fully awaken during these arousals, based on the detection by other electronic means (electrocardiographic variation). Some suggested that micro-arousals could alter sleep architecture and thus causing daytime symptoms and neurocognitive dysfunction.

Growth failure

Marcus et al[30] evaluated 14 prepubertal children (mean, 4 years) who had OSA documented by overnight PSG. Energy intake, sleeping energy expenditure, and anthropomorphic measurements were taken before and after adenotonsillectomy. The mean sleeping energy expenditure decreased with a mean weight Z score increasing postoperatively without any change in energy intake. Our previous case-control resting energy expenditure study found a trend towards higher energy consumption in the OSA group, but we could not establish a correlation between severity of OSA and the energy expenditure.[31] Bar et al[32] evaluated changes in growth of the child and also measured the insulin-like growth factor I before and 18 months after an adenotonsillectomy. There was a statistically significant increase in the weight and the growth factor I levels at 18 months. The pathogenesis associated with the failure to thrive among children with OSA is likely to be an interplay between various mechanisms. Luckily this complication is being seen less because people are becoming more aware of this condition and seek early medical intervention.

Cardiovascular abnormalities

In adults, the presence of OSA is directly associated with an increased risk of systemic hypertension.[33] Cyclical hypoxia during sleep with alterations in the renin-angiotensin axis and enhanced sympatho-adrenal release is proposed as the underlying mechanism for the hypertension.[34] However, very few studies have addressed this issue in children. Tal et al[35] used radionuclide ventriculography to evaluate ventricular function in 27 children referred for oropharyngeal obstruction who had symptoms suggestive of OSA. They found decreased right ventricular ejection fraction in 37% of these children and abnormal wall motion in 67%. Eleven patients who had adenotonsillectomy showed improvement after a repeat evaluation. Left ventricular hypertrophy and abnormal geometry have also been documented in both children and adolescents with OSA.[36]

Systemic blood pressure was evaluated in a study of

children referred for PSG.[37] Higher diastolic pressures (adjusted for body mass index and age) were found in children with OSA compared with those who had primary snoring. In a recent study using 24-hour ambulatory blood pressure monitoring, abnormal blood pressure variability, higher night-to-day systolic pressure, and a smaller nocturnal dip in mean blood pressure were documented. The authors also found a notable association between the abnormal blood pressure and the frequency of obstructive apnoeas, oxygen desaturation, and arousal.[38] Primary snoring has also been reported to be associated with cardiovascular morbidity. A local study showed abnormal arterial distensibility and blood pressure in children diagnosed as having primary snoring.[39]

Mortality

Adults with OSA have been reported to be at an increased risk of premature death, compared with the general population, mainly from respiratory and cardiovascular complications. Hypertension, obesity, an age of between 30 and 50 years, and a severe degree of OSA all increase the risk of early death in these patients.[40] The mortality rate of childhood OSA is unknown, but the deaths thought to be secondary to OSA occurred during the time when this condition was relatively unrecognised and were attributed to perioperative cardiorespiratory failure in children with associated craniofacial and neurological disorders.[41] A definitive causative relationship between sudden infant death and OSA has not been established. However, an association between SDB and apparent life-threatening events has been suggested.[42]

Diagnosis

Obstructive sleep apnoea is unlikely in the absence of habitual snoring, but the symptoms on their own, however, will yield a poor diagnosis.[43] Results of a physical examination are often normal and there may be non-specific findings related to adenotonsillar hypertrophy (eg mouth breathing and adenoidal facies) and evidence of OSA complications may be present (eg systemic hypertension). However, the size of tonsils and the adenoids on direct inspection are not related to the presence or severity of OSA.[44]

It is important to identify children with OSA early to minimise the chance of developing further complications. Early recognition and intervention has considerable health care resources implication as well.[45,46] The 'gold standard' for the diagnosis of OSA is overnight PSG but it has not been properly standardised with regard to its performance and interpretation, especially among the paediatric population. Normative standards for PSG determination have been chosen on the basis of the statistical distribution of data,[47-49] but validity of these standards as predictors of the long-term outcome has not been established. The use of different clinical and laboratory measurement procedures and diagnostic criteria has made intergroup comparison difficult, if not impossible. The recently published Clinical Practice Guideline for Diagnosis and Management of Childhood Obstructive Sleep Apnea Syndrome (2002) by the American Academy of Pediatrics concluded that PSG is very poorly validated and the normalised data in children have not been shown to be reliable as predictors for the presence of complications. The use of PSG becomes even more dubious because of its heavy focus on breathing and minimal measures of sleep quality.[3]

The most acceptable diagnostic cut-off for childhood OSA as proposed by Marcus et al[47] is an obstructive apnoea index of greater than 1 episode per hour. This criterion, however, does not take into account episodes of hypopnoea that are relevant in children with OSA. The same group recently proposed an apnoea-hypopnoea index of greater than 1.5 episodes per hour as diagnostic for OSA.[50]

Incorrectly diagnosing OSA as primary snoring in adults after a single night recording has been reported in some studies.[51-53] A disturbed sleep pattern caused by an artificial sleep laboratory environment and continuous visual surveillance is well described and is known as the 'first night effect' (FNE), which may influence the reliability of the results from a single night study.[53-55] The FNE is known to reduce the amount of REM sleep and with childhood OSA being more severe during REM sleep, a single night PSG may be expected to generate a high rate of false negative results. Katz et al[56] performed PSG on 30 snoring children (mean age, 4.1 years) and found that the clinical diagnosis of either OSA or primary snoring remained the same in all subjects tested. No statistically significant differences in sleep or respiratory variables were observed between the nights except for the percentage of total sleep time in stage 2 sleep which was slightly higher on the second night. The sleep assessments, however, were not performed on consecutive nights and were done 7 to 27 days apart; hence, each of these nights in the laboratory could be considered as a first night. We recently carried out a study looking at the occurrence of FNE and feasibility of a single night study as the assessment of OSA in children. The FNE was clearly demonstrated but the PSG correctly identified 84.6% of OSA cases and all cases missed by the first night study had only borderline PSG abnormality. Hence, a single night sleep study is adequate and more cost-effective in assessing childhood OSA.[57]

A variety of screening tests have also been proposed, including pulse oximetry, abbreviated sleep study, audiotaping, and radiography. These tests were compared with PSG with its inherent problems as mentioned above. Most tests were found to have an acceptable positive predictive value but less than desirable specificity and negative predictive value. A study that we conducted on 242 children suspected of having OSA evaluated the usefulness of a screening questionnaire in predicting cases of PSG-confirmed OSA. Three questions were found

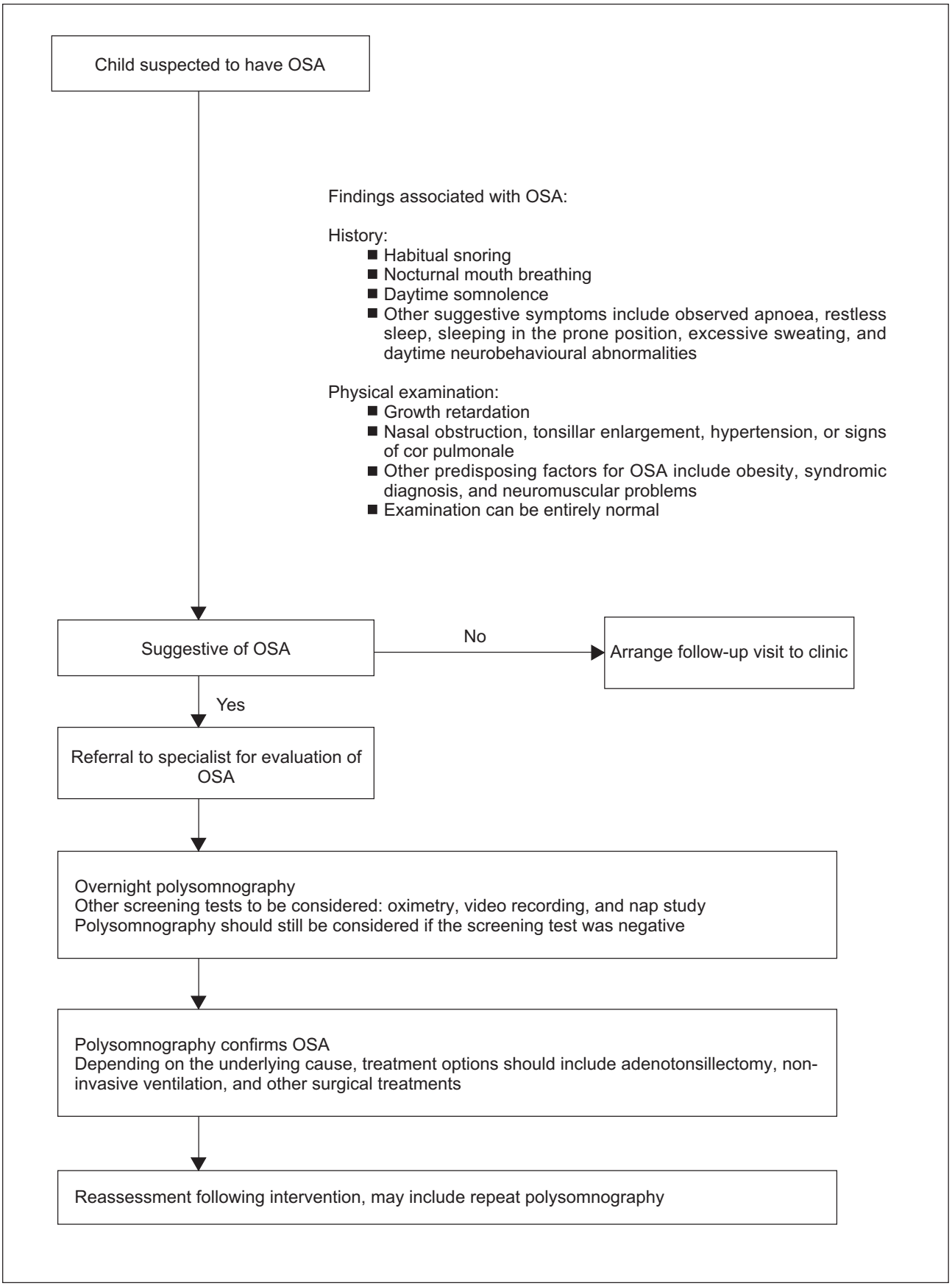

Fig. Flowchart for the management of childhood obstructive sleep apnoea (OSA)

to be highly relevant for predicting the presence of this condition: nocturnal mouth breathing, snoring, and fatigue in daytime (unpublished data).

Treatment

Medical treatment

Nasal corticosteroids have recently been examined as an alternative to adenotonsillectomy in otherwise healthy children with OSA. Brouillette et al[58] in a prospective, randomised, and double-blind study treated children with mild-to-moderate OSA with a 6-week course of either nasal corticosteroids or a placebo. The authors were able to demonstrate a moderate improvement in cases treated with nasal corticosteroids. The apnoea-hypopnoea index decreased from 11 episodes to 6 episodes per hour. This was associated with concomitant decreases of about 50% in both the desaturation index and the movement arousal index. In contrast, the placebo group did not show any improvements. The report, however, was unable to show notable changes in adenoidal size assessed by lateral neck radiograph. Wheeler and van Someren[59] found a notable improvement in the symptom scores of 40% to 50% of subjects treated with 4 months of nasal fluticasone (200 μg/d), but formal assessment using overnight PSG was not mentioned. Kiely et al[60] were also able to demonstrate beneficial effects in patients with OSA and rhinitis treated with a 4-week course of intranasal fluticasone. Nasal corticosteroids work by exerting a lympholytic action on the inflammation and upper airway oedema. Demain and Goetz[61] demonstrated that nasal corticosteroids over a 24-week treatment period reduced adenoidal size and improved symptoms of nasal airway obstruction. Topical intranasal steroids may become the alternative therapy for some children with mild OSA.

Surgical treatment

There are many published papers, primarily case reports and case series, supporting the efficacy of tonsillectomy with or without adenoidectomy as treatment for OSA. One of the problems associated with these published studies, however, is the use of different end-points in the assessment of the outcome.[18] A few studies provided evidence that adenotonsillectomy is superior to either adenoidectomy or tonsillectomy alone.[62,63] Summarising the results from all published studies seems to find that adenotonsillectomy is curative in around 85% of children, even if they are obese. Some children, with persistent problems after adenotonsillectomy, may benefit from further uvulopalatopharyngoplasty, maxillary or mandibular surgery, or tracheostomy. Alternative surgical procedures for OSA in children were well reviewed in a recently published paper.[64] It is our practice to review patients who have undergone adenotonsillectomy at 4 to 6 months after the operation. If they remain symptomatic, a repeat PSG will be offered and mechanical intervention will be instituted if residual OSA is demonstrated. The following group of patients have been identified to be at a higher risk for a residual problem: those with initial severe OSA, obesity, and a positive family history of OSA.[3] In a study by Contencin et al,[65] 8.5% of children who had undergone adenotonsillectomy experienced residual or recurrent symptoms of OSA 3 years postoperatively. In a recently published local study,[66] boys undergoing surgical adenotonsillectomy at an early age (<5 years) were found to be at a higher risk for residual OSA.

Mechanical treatment

In childhood OSA, nasal continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) have established themselves as the second-line treatment or in cases where adenotonsillectomy is contra-indicated.[67-69] Nasal CPAP to the lumen of the airway decreases airway collapsibility. It is of utmost importance that the initial approach to the family and children be performed correctly and successfully. Nasal CPAP therapy should be titrated during PSG to determine effective pressures, and children on CPAP therapy should be followed up regularly to ensure compliance and the proper fitting of equipments.

Bilevel positive airway pressure also allows setting of a backup rate, and provides some ventilatory assistance. This is especially important for patients with sleep-related hypoventilation caused by muscle weakness, neurological disease, or obesity. The evaluation of compliance and tolerability of either CPAP or BiPAP in children is lacking. A recently published randomised, double-blind clinical trial comparing CPAP with BiPAP for the treatment of OSA in adults did not find any notable differences in compliance between the two groups.[70] One potential complication of long-term nasal mask CPAP or BiPAP is mid-face hypoplasia,[71] and children on these treatments should be monitored carefully and regularly for abnormal maxillomandibular growth.

A proposed scheme for the management of childhood OSA is shown in the Fig. Despite the confusion and lack of standardised data of childhood OSA, recent realisations that the scope of the condition is wider, the symptomatology is broader, and the diagnosis is not as straightforward as previously thought are already important advancements. A lot more work on clinical features, pathophysiology, diagnosis, and treatment including the full range of symptoms caused by increased upper airway resistance is required. Further research work should give a better insight of the origins of adult morbidity resulting from childhood sleep-related breathing problem and how it can be prevented. As our knowledge on this condition increases, more questions are going to be generated. Further advances in this important field of paediatric medicine can only be made with international collaborative research using evidence-based definitions, standardised techniques, and diagnostic criteria.

References

1. Standards and indications for cardiopulmonary sleep studies in children. American Thoracic Society. Am J Respir Crit Care Med 1996; 153:866-78.
2. Guilleminault C, Khramtsov A. Upper airway resistance syndrome in children: a clinical review. Semin Pediatr Neurol 2001;8:207-15.
3. Schechter MS; Section on Pediatric Pulmonology, Subcommittee on Obstructive Sleep Apnea Syndrome. Technical report: diagnosis and management of childhood obstructive sleep apnea syndrome. Pediatrics 2002;109:E69.
4. Wing YK, Hui SH, Pak WM, et al. A controlled study of sleep related disordered breathing in obese children. Arch Dis Child 2003;88: 1043-7.
5. Chau KW, Ng DK, Kwok CK, Chow PY, Ho JC. Clinical risk factors for obstructive sleep apnoea in children. Singapore Med J 2003;44: 570-3.
6. Ali NJ, Pitson D, Stradling JR. Natural history of snoring and related behaviour problems between the ages of 4 and 7 years. Arch Dis Child 1994;71:74-6.
7. Topol HI, Brooks LJ. Follow-up of primary snoring in children. J Pediatr 2001;138:291-3.
8. Marcus CL, Hamer A, Loughlin GM. Natural history of primary snoring in children. Pediatr Pulmonol 1998;26:6-11.
9. Ali NJ, Pitson DJ, Stradling JR. Snoring, sleep disturbance, and behaviour in 4-5 year olds. Arch Dis Child 1993;68:360-6.
10. Gislason T, Benediktsdottir B. Snoring, apneic episodes, and nocturnal hypoxemia among children 6 months to 6 years old. An epidemiologic study of lower limit of prevalence. Chest 1995;107:963-6.
11. Redline S, Tishler PV, Schluchter M, Aylor J, Clark K, Graham G. Risk factors for sleep-disordered breathing in children. Associations with obesity, race, and respiratory problems. Am J Respir Crit Care Med 1999;159:1527-32.
12. Rosen CL, Larkin EK, Kirchner HL, et al. Prevalence and risk factors for sleep-disordered breathing in 8- to 11-year-old children: association with race and prematurity. J Pediatr 2003;142:383-9.
13. Tal A, Bar A, Leiberman A, Tarasiuk A. Sleep characteristics following adenotonsillectomy in children with obstructive sleep apnea syndrome. Chest 2003;124:948-53.
14. Rosen CL. Clinical features of obstructive sleep apnea hypoventilation syndrome in otherwise healthy children. Pediatr Pulmonol 1999;27: 403-9.
15. Li AM, Hui S, Wong E, Cheung A, Fok TF. Obstructive sleep apnoea in children with adenotonsillar hypertrophy: prospective study. Hong Kong Med J 2001;7:236-40.
16. Ferreira AM, Clemente V, Gozal D, et al. Snoring in Portuguese primary school children. Pediatrics 2000;106:E64.
17. Gozal D, Wang M, Pope DW Jr. Objective sleepiness measures in pediatric obstructive sleep apnea. Pediatrics 2001;108:693-7.
18. Lipton AJ, Gozal D. Treatment of obstructive sleep apnea in children: do we really know how? Sleep Med Rev 2003;7:61-80.
19. Goh DY, Galster P, Marcus CL. Sleep architecture and respiratory disturbances in children with obstructive sleep apnea. Am J Respir Crit Care Med 2000;162:682-6.
20. Gozal D. Sleep-disordered breathing and school performance in children. Pediatrics 1998;102:616-20.
21. Weissbluth M, Davis AT, Poncher J, Reiff J. Signs of airway obstruction during sleep and behavioral, developmental, and academic problems. J Dev Behav Pediatr 1983;4:119-21.
22. Chervin RD, Dillon JE, Bassetti C, Ganoczy DA, Pituch KJ. Symptoms of sleep disorders, inattention, and hyperactivity in children. Sleep 1997;20:1185-92.
23. Friedman BC, Hendeles-Amitai A, Kozminsky E, et al. Adenotonsillectomy improves neurocognitive function in children with obstructive sleep apnea syndrome. Sleep 2003;26:999-1005.
24. Ali NJ, Pitson D, Stradling JR. Sleep disordered breathing: effects of adenotonsillectomy on behaviour and psychological functioning. Eur J Pediatr 1996;155:56-62.
25. Blunden S, Lushington K, Kennedy D, Martin J, Dawson D. Behavior and neurocognitive performance in children aged 5-10 years who snore compared to controls. J Clin Exp Neuropsychol 2000;22:554-68.
26. Goldstein NA, Post JC, Rosenfeld RM, Campbell TF. Impact of tonsillectomy and adenoidectomy on child behavior. Arch Otolaryngol Head Neck Surg 2000;126:494-8.
27. Gozal D, Daniel JM, Dohanich GP. Behavioural and anatomical correlates of chronic episodic hypoxia during sleep in the rat. J Neurosci 2001;21:2442-50.
28. Li RC, Row BW, Gozal E, et al. Cyclooxygenase 2 and intermittent hypoxia-induced spatial deficits in the rat. Am J Respir Crit Care Med 2003;168:469-75.
29. Katz ES, Lutz J, Black C, Marcus CL. Pulse transit time as a measure of arousal and respiratory effort in children with sleep-disordered breathing. Pediatr Res 2003;53:580-8.
30. Marcus CL, Carroll JL, Koerner CB, Hamer A, Lutz J, Loughlin GM. Determinants of growth in children with the obstructive sleep apnea syndrome. J Pediatr 1994;125:556-62.
31. Li AM, Yin J, Chan D, Hui S, Fok TF. Sleeping energy expenditure in paediatric patients with obstructive sleep apnoea syndrome. Hong Kong Med J 2003;9:353-6.
32. Bar A, Tarasiuk A, Segev Y, Phillip M, Tal A. The effect of adenotonsillectomy on serum insulin-like growth factor-I and growth in children with obstructive sleep apnea syndrome. J Pediatr 1999;135:76-80.
33. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 2000;342:1378-84.
34. Fletcher EC. Effect of episodic hypoxia on sympathetic activity and blood pressure. Respir Physiol 2000;119:189-97.
35. Tal A, Leiberman A, Margulis G, Sofer S. Ventricular dysfunction in children with obstructive sleep apnea: radionuclide assessment. Pediatr Pulmonol 1988;4:139-43.
36. Amin RS, Kimball TR, Bean JA, et al. Left ventricular hypertrophy and abnormal ventricular geometry in children and adolescents with obstructive sleep apnea. Am J Respir Crit Care Med 2002; 165:1395-9.
37. Marcus CL, Greene MG, Carroll JL. Blood pressure in children with obstructive sleep apnea. Am J Respir Crit Care Med 1998; 157:1098-103.
38. Amin RS, Carroll JL, Jeffries JL, et al. Twenty-four-hour ambulatory blood pressure in children with sleep-disordered breathing. Am J Respir Crit Care Med 2004;169:950-6.
39. Kwok KL, Ng DK, Cheung YF. BP and arterial distensibility in children with primary snoring. Chest 2003;123:1561-6.
40. Lavie P, Herer P, Peled R, et al. Mortality in sleep apnea patients: a multivariate analysis of risk factors. Sleep 1995;18:149-57.
41. Lauritzen C, Lilja J, Jarlstedt J. Airway obstruction and sleep apnea in children with craniofacial anomalies. Plast Reconstruct Surg 1986; 77:1-6.
42. Guilleminault C, Pelayo R, Leger D, Philip P, Ohayon M. Sleep-disordered breathing and upper-airway anomalies in first-degree relatives of ALTE children. Pediatr Res 2001;50:14-22.
43. Carroll JL, McColley SA, Marcus CL, Curtis S, Loughlin GM. Inability of clinical history to distinguish primary snoring from obstructive sleep apnea syndrome in children. Chest 1995;108:610-8.
44. Li AM, Wong E, Kew J, Hui S, Fok TF. Use of tonsil size in the evaluation of obstructive sleep apnoea. Arch Dis Child 2002;87:156-9.
45. Tarasiuk A, Simon T, Tal A, Reuveni H. Adenotonsillectomy in children with obstructive sleep apnea syndrome reduces health care utilization. Pediatrics 2004;113:351-6.
46. Reuveni H, Simon T, Tal A, Elhayany A, Tarasiuk A. Health care services utilization in children with obstructive sleep apnea syndrome. Pediatrics 2002;110:68-72.
47. Marcus CL, Omlin KJ, Basinki DJ, et al. Normal polysomnographic values for children and adolescents. Am Rev Respir Dis 1992;146: 1235-9.
48. Uliel S, Tauman R, Greenfeld M, Sivan Y. Normal polysomnographic respiratory values in children and adolescents. Chest 2004;125:872-8.
49. Rosen CL, D'Andrea L, Haddad GG. Adult criteria for obstructive sleep apnea do not identify children with serious obstruction. Am Rev Respir Dis 1992;146:1231-4.

50. Witmans MB, Keens TG, Davidson Ward SL, Marcus CL. Obstructive hypopneas in children and adolescents: normal values. Am J Respir Crit Care Med 2003;168:1540.
51. Bliwise DL, Benkert RE, Ingham RH. Factors associated with nightly variability in sleep-disordered breathing in the elderly. Chest 1991;100:973-6.
52. Mosko SS, Dickel MJ, Ashurst J. Night-to-night variability in sleep apnea and sleep-related periodic leg movements in the elderly. Sleep 1988;11:340-8.
53. Aber WR, Block AJ, Hellard DW, Webb WB. Consistency of respiratory measurements from night to night during the sleep of elderly men. Chest 1989;96:747-51.
54. Le Bon O, Hoffmann G, Tecco J, et al. Mild to moderate sleep respiratory events: one negative night may not be enough. Chest 2000; 118:353-9.
55. Agnew HW Jr, Webb WB, Williams RL. The first night effect: an EEG study of sleep. Psychophysiology 1966;2:263-6.
56. Katz ES, Greene MG, Carson KA, et al. Night-to-night variability of polysomnography in children with suspected obstructive sleep apnea. J Pediatr 2002;140:589-94.
57. Li AM, Wing YK, Cheung A, Chan D, et al. Is two-night polysomnographic study necessary in childhood sleep-related disordered breathing. Chest. In press.
58. Brouillette RT, Manoukian JJ, Ducharme FM, et al. Efficacy of fluticasone nasal spray for pediatric obstructive sleep apnea. J Pediatr 2001;138:838-44.
59. Wheeler AJ, van Someren V. Fluticasone for obstructive sleep apnea. J Pediatr 2002;140:489.
60. Kiely JL, Nolan P, McNicholas WT. Intranasal corticosteroid therapy for obstructive sleep apnoea in patients with co-existing rhinitis. Thorax 2004;59:50-5.
61. Demain JG, Goetz DW. Pediatric adenoidal hypertrophy and nasal airway obstruction: reduction with aqueous nasal beclomethasone. Pediatrics 1995;95:355-64.
62. Zucconi M, Strambi LF, Pestalozza G, Tessitore E, Smirne S. Habitual snoring and obstructive sleep apnea syndrome in children: effects of early tonsil surgery. Int J Pediatr Otorhinolaryngol 1993; 26:235-43.
63. Nieminen P, Tolonen U, Lopponen H. Snoring and obstructive sleep apnea in children: a 6-month follow-up study. Arch Otolaryngol Head Neck Surg 2000;126:481-6.
64. Cohen SR, Holmes RE, Machado L, Magit A. Surgical strategies in the treatment of complex obstructive sleep apnoea in children. Paediatr Respir Rev 2002;3:25-35.
65. Contencin P, Guilleminault C, Manach Y. Long-term follow-up and mechanisms of obstructive sleep apnea (OSA) and related syndromes through infancy and childhood. Int J Pediatr Otorhinolaryngol 2003; 67(Suppl 1):119S-23S.
66. Chau KW, Ng KK, Kwok KL, Cheung MY. Survey of children with obstructive sleep apnea syndrome in Hong Kong of China. Chin Med J (Engl) 2004;117:657-60.
67. Marcus CL, Ward SL, Mallory GB, et al. Use of nasal continuous positive airway pressure as treatment of childhood obstructive sleep apnea. J Pediatr 1995;127:88-94.
68. Waters KA, Everett FM, Bruderer JW, Sullivan CE. Obstructive sleep apnea: the use of nasal CPAP in 80 children. Am J Respir Crit Care Med 1995;152:780-5.
69. Guilleminault C, Nino-Murcia G, Heldt G, Baldwin R, Hutchinson D. Alternative treatment to tracheostomy in obstructive sleep apnea syndrome: nasal continuous positive airway pressure in young children. Pediatrics 1986;78:797-802.
70. Gay PC, Herold DL, Olson EJ. A randomized, double-blind clinical trial comparing continuous positive airway pressure with a novel bilevel pressure system for treatment of obstructive sleep apnea syndrome. Sleep 2003;26:864-9.
71. Li KK, Riley RW, Guilleminault C. An unreported risk in the use of home nasal continuous positive airway pressure and home nasal ventilation in children: mid-face hypoplasia. Chest 2000; 117:916-8.