

American Thoracic Society

MEDICAL SECTION OF THE AMERICAN LUNG ASSOCIATION

Cardiorespiratory Sleep Studies in Children

Establishment of Normative Data and Polysomnographic Predictors of Morbidity

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The obstructive sleep apnea syndrome (OSAS) has been studied extensively in adults. However, it is only more recently that OSAS has been evaluated scientifically in children (1). It is now recognized that childhood OSAS is common (estimated prevalence of 1–3% in preschool children [2, 3]), and can result in significant morbidity. Because childhood OSAS differs from adult OSAS in its etiology, clinical manifestations, polysomnographic characteristics, and sequelae, studies derived from adult patients cannot be extrapolated to children. The clinical manifestations of OSAS in children can include snoring, labored breathing during sleep, nocturnal enuresis, hyperactivity, and attention deficit. Daytime hypersomnolence is sometimes observed but not as frequently as in adults.

Over the past few years, the burgeoning interest in childhood OSAS has resulted in a large increase in the number of published scientific studies on the topic. Nevertheless, there are major gaps in the medical and scientific literature regarding important aspects of the management of these patients. Many treatment protocols are based on empirical evidence or anecdotal reports, rather than well-designed and controlled studies. As a result, there is no consensus on the management of children with OSAS, and wide discrepancies in management approaches are found among different centers. Therefore, the American Thoracic Society convened a workshop in April 1998 to discuss these issues, in the hope that pooling available knowledge would help define important areas for study, lead to consistent and uniform methodological approaches so that data can be compared between different institutions, and lay the groundwork for a future multicenter study to examine important issues.

OBJECTIVES

The objectives of the workshop were as follows:

1. To evaluate critically the existing literature on normative values of cardiorespiratory sleep parameters in children
2. To determine predicted morbidity associated with various degrees of respiratory abnormalities during sleep; morbidity in cardiovascular function, growth, neurocognitive function, and behavior was included, as well as the predicted postoperative morbidity and recurrence of obstructive sleep apnea after standard treatments
3. To define areas in which further investigation is needed to determine normal values and predictors of morbidity
4. To develop and organize a multicenter commitment to obtain the required data

1. ARE THERE ADEQUATE NORMATIVE DATA ON POLYSOMNOGRAPHIC PARAMETERS IN CHILDREN?

Although consensus exists for electroencephalogram (EEG) scoring and sleep staging in adults (4) and young infants (5), a formal consensus has never been obtained for children and adolescents. Several studies in this age group are available, and in some of these studies subjects were evaluated for several nights (for review, see Reference 6). Therefore, a critical assessment of published data may allow for the development of normative criteria for the EEG during sleep in children. Since the distribution and duration of sleep/wake states change with maturation, normative data must be obtained in large enough groups at various ages to define these changes. Normative data for arousals from sleep are scanty in children, and there is controversy as to whether the standard American Sleep Disorders Association criteria for defining arousals (6) should be used (7).

Normative respiratory data during sleep are far more controversial. Although a number of studies are available, they are based on relatively small sample sizes, and do not necessarily address the ages at which childhood OSAS is most prevalent (8–11). On the basis of normative data, an obstructive apnea index of 1 is often chosen as the cutoff for normality. However, while an apnea index of 1 is *statistically* significant (i.e., at the 97.5th percentile for an asymptomatic, normative population), it is not known what level is *clinically* significant. Sleep-disordered breathing in childhood consists of a spectrum of disease, ranging from primary snoring to upper airway resistance syndrome, obstructive hypoventilation, and obstructive sleep apnea. Parameters for defining these conditions have not been established. Furthermore, few normative data are available for some of the important factors required in establishing these diagnoses, such as hypopneas (9), degree of paradoxical inward rib cage movement during inspiration (12), and esophageal pressure swings (13). Evaluation of the existing data is complicated by the lack of standardization of polysomnographic practices.

2. CURRENT DATA REGARDING MORBIDITY ASSOCIATED WITH CHILDHOOD OSAS

Cardiovascular Complications

The early reports of childhood OSAS frequently mentioned the presence of pulmonary hypertension (14–17), resulting from recurrent nocturnal hypoxemia, hypercarbia, and respiratory acidosis. This can lead to cor pulmonale and congestive heart failure. Left ventricular dysfunction has also been reported (16, 18, 19). Brouillette and coworkers (14) reported cor pulmonale in 55% of 22 patients with OSAS, and Guilleminault and coworkers (20) reported cardiac or cardiorespiratory failure in 20% of 50 patients. These statistics probably do not re-

flect current medical care, as the increased level of awareness of OSAS among pediatricians has resulted in earlier diagnosis of patients. The consensus of the panel was that *cor pulmonale* is rarely seen these days. However, more up-to-date statistics are not available. Wilkinson and colleagues (21) found electrocardiogram (ECG) evidence of right heart strain in 3% of 92 children scheduled for tonsillectomy and/or adenoidectomy; those with abnormal electrocardiograms had symptoms of OSAS. Tal and coworkers (18) used radionuclide ventriculography to demonstrate a reduced right ventricular ejection fraction in 37% of children with clinically diagnosed OSAS, although only 7% had clinical evidence of pulmonary hypertension. This study suggests that asymptomatic degrees of pulmonary hypertension may be more common than previously thought. Further studies, using sensitive and specific techniques, are needed, and the role of echocardiography should be further explored. When *cor pulmonale* does develop, it is readily reversed by treatment of the OSAS (15, 17, 18, 21). Post-operative pulmonary edema is a well-described complication of tonsillectomy and adenoidectomy in children with OSAS (22). The mechanism is unclear.

Children with OSAS may develop marked sinus arrhythmia and bradycardia, but other types of arrhythmias appear to be rare (23). The paucity of arrhythmias compared with adults is probably due to the lack of underlying coronary artery disease or other cardiac conditions in children. Children with OSAS have a characteristic pattern of heart rate variability during sleep, which is suggestive of significant alterations in autonomic nervous system tone variability (24). Hypoxemia during obstructive events results in statistically significant changes in heart rate variations, but these have been considered clinically insignificant by some investigators (23). Changes in autonomic function due to repetitive hypoxemia, hypercapnia, or arousal may predispose some children toward the occurrence of arrhythmias, and may also facilitate the activation of adaptive mechanisms that may be involved in decreased baroreceptor sensitivity and increasing blood pressure. However, data in children are lacking.

In general, hypertension is less common in children than adults, and therefore would be less expected in children with OSAS. However, a number of cases of children with hypertension related to OSAS have been reported in the literature (1, 19, 25, 26). In most cases, OSAS was severe. One study measured blood pressure in consecutive children with primary snoring or OSAS, and found that children with OSAS had increased blood pressure during sleep (27). The degree of hypertension correlated with the apnea index, as well as with the degree of obesity. This study raises the concern that children with undiagnosed OSAS may develop longstanding elevations in blood pressure, which could result in increased risk of cardiovascular complications later in life.

Growth Failure

Failure to thrive (growth less than the fifth percentile for age) is a well known complication of childhood OSAS. The earlier literature was based primarily on case reports or chart reviews that described the most severely affected patients, many of whom had underlying medical disorders. With the current increased awareness of childhood OSAS, and enhanced ability to detect milder cases by polysomnography, the majority of children now identified are diagnosed before severe complications develop, and failure to thrive is seen less frequently. Many reports of failure to thrive included a high proportion of very young children with severe OSAS and underlying conditions such as trisomy 21, craniofacial anomalies, or neuromuscular diseases (14, 20, 28, 29). However, studies of children with

out underlying medical conditions have shown that somatic growth can be impaired in childhood OSAS without causing failure to thrive. Studies of children without underlying medical conditions have shown an increased weight gain velocity in the majority of children after surgical correction of OSAS (30-32). Growth impairment in childhood OSAS is not well understood. Proposed mechanisms include the following: (1) poor caloric intake associated with adenotonsillar hypertrophy, (2) excessive caloric expenditure secondary to increased work of breathing (32), (3) abnormal growth hormone release secondary to loss of deep non-REM sleep (33), and (4) lack of end organ responsiveness to growth factors (34). The relative roles of these factors are unclear. One study failed to demonstrate a change in caloric intake in children with OSAS who had increased growth after treatment (32). Although resting energy expenditure during sleep is significantly increased in children with OSAS, the increase is relatively small and probably does not account totally for the impaired growth (32). The role of growth hormone is unclear. There is a single report of reversible growth hormone deficiency in an achondroplastic child with severe OSAS and profound sleep fragmentation (33). However, a larger study of children with achondroplasia did not confirm this (35).

In summary, although the impact of OSAS on growth has been well described, there are no population-based studies demonstrating the true prevalence of failure to thrive. In the United States, failure to thrive is infrequent in OSAS except in children with underlying medical conditions or in children who present at a younger age (less than 3 yr). However, catch-up growth, as indicated by an increase in weight gain velocity after surgical correction of OSAS, appears common. Although failure to thrive appears to be related to the severity of OSAS, precise risk factors have not been determined, and the mechanisms for growth failure are poorly understood.

Neurocognitive Morbidity

Numerous studies have shown that sleep fragmentation and hypoxemia can result in neurocognitive changes in adults. Experimental fragmentation of the sleep of healthy, normal adults may be achieved by auditory-induced arousals. Subjects who were awakened at intervals during the night demonstrated performance decrements and increased sleepiness on the following day. This was also true when EEG arousals, rather than behavioral arousals, were induced (36-38). The physiological and behavioral effects of partial and total sleep loss by OSAS in adults have been investigated extensively. Daytime tiredness or fatigue is a common complaint, although sleepiness, being a subjective complaint, may not be directly reported. Significant deterioration in functions requiring concentration or dexterity, automatic behavior with retrograde amnesia, disorientation, and morning confusion have all been reported, and led to the term "sleep drunkenness." In addition, personality changes and abnormal behavioral outbursts after sleep fragmentation, aggression, irritability, anxiety attacks, and depression may all occur. Hypoxemia has been shown to affect psychomotor processing, executive functioning, and intellectual function (39, 40).

It would be expected that sleep fragmentation and hypoxemia would affect the neuropsychological and cognitive performance of children, as in adults. In fact, because a young child is going through a period of rapid learning and development, the impact of abnormal sleep may be even greater. Reports of decreased intellectual function in children with tonsillar and adenoidal hypertrophy date from 1889, when Hill reported on "some causes of backwardness and stupidity in

children" (41). School problems have been reported repeatedly in case series of children with OSAS, which may in fact underlie more extensive behavioral disturbances such as restlessness, aggressive behavior, excessive daytime sleepiness, and poor test performance (42).

Daytime sleepiness occurs less frequently in children with OSAS than in adults with OSAS. In one study, the incidence of excessive daytime sleepiness in a cohort of children with either primary snoring or OSAS was similar, and daytime sleepiness was identified in only 20% (43). Other studies have reported excessive daytime sleepiness in 8–62% of children with OSAS (44). The variable prevalence of excessive daytime sleepiness may reflect referral biases, e.g., patients with a chief complaint of sleepiness may be more likely to present to a neurology-based clinic, whereas patients with a complaint of snoring may be more likely to present to a pulmonary-based clinic. Nevertheless, it is clear that excessive daytime sleepiness is less common in children with OSAS than in adults with OSAS. This may be because children with OSAS are less prone than adults to develop sleep fragmentation (45, 46). The paucity of data correlating the extent of physiological alterations during sleep and the severity of daytime sleepiness or behavioral disturbances in children precludes the formulation of any definitive conclusions or recommendations.

The neurocognitive and behavioral consequences of disrupted sleep architecture and hypoxemia in children with OSAS have not yet been defined by appropriate scientific methodology in the pediatric population (47, 48). However, a few studies have documented that children with sleep disorders tend to have behavioral problems similar to those observed in children with attention deficit hyperactivity disorder. In fact, sleep disturbance was identified in the DSM-III as a criterion for diagnosis, although this was subsequently dropped with the publication of DSM-IV. One review has emphasized that recognizing the possible presence of sleep apnea is essential for accurate diagnosis and treatment of children with psychological difficulties (49). A survey of 782 children documented daytime sleepiness, hyperactivity, and aggressive behavior in children who snored, with 27 and 38% of children at high risk for a sleep or breathing disorder displaying clinically significant levels of inattention and hyperactive behavior, respectively (50). Similar studies in smaller patient cohorts with proven OSAS have also documented parental reports of behavioral disturbances, which improve after treatment of OSAS (20, 31, 51, 52). So far, a few studies have attempted to quantify, albeit in a limited number of pediatric patients with OSAS, the extent of neurocognitive dysfunction associated with OSAS. One such study found inverse correlations between memory and learning performance and the apnea hypopnea index in 14 morbidly obese children (53). In another study, 12 children (mean age, 7.5 yr) with moderate to severe OSAS showed significant postsurgical reductions in inattention and improvement in vigilance on a continuous performance task after surgical treatment (54). In addition, these children also showed a reduction in aggressive and hyperactive behaviors as measured by the Conners Parent Rating Scale (54). Gozal (55) demonstrated an unusually high prevalence (18%) of snoring and nocturnal gas exchange abnormalities in a cohort of 297 children who were functioning in the lowest (10th) percentile of their class. Those children who received treatment showed an improvement in academic performance.

In summary, although empirical awareness of the deleterious consequences of OSAS on neurocognitive function and behavior is well established, few scientific studies have examined the cause-effect relationship between these two elements.

Predictors of Immediate Postoperative Complications in Children with OSAS

Tonsillectomy and adenoidectomy (T&A) is the standard first-line treatment for childhood OSAS, resulting in a cure in the majority of patients (56). However, children with OSAS are at greater postoperative risk for respiratory compromise than children undergoing T&A for other indications. Postoperative respiratory complications include transient worsening of OSAS secondary to postoperative edema and increased secretions; respiratory depression from anesthetic agents, narcotics, and the use of oxygen in children with a blunted hypoxic ventilator-y drive; and the occurrence of postobstructive pulmonary edema. In addition, preoperative sedation may precipitate acute upper airway obstruction. The medical literature contains several studies that identify risk factors for perioperative respiratory compromise after T&A in children with OSAS. Most studies were retrospective, and few of these studies used polysomnographic data to stratify the severity of OSAS.

McColley and coworkers (57) retrospectively reviewed the postoperative course of children who underwent T&A for polysomnographically proven OSAS. Key risk factors for respiratory compromise after surgery were young age (less than 3 yr) and respiratory disturbance index (RDI) > 10. Rosen and colleagues (58) used polysomnographic data to identify patients at risk for postoperative respiratory complications, and found that an RDI > 40 and arterial oxygen saturation nadir < 70% were risk factors. The preceding studies, along with more recent reviews of larger numbers of children after T&A (59, 60), have identified clinical features of children who are more likely to have respiratory complications after adenotonsillectomy for sleep apnea. These clinical features include young age, failure to thrive, cor pulmonale, presence of neuromotor disease (hypotonia, cerebral palsy, seizures, etc.), craniofacial abnormalities (Down syndrome, achondroplasia, and other syndromes), chromosomal abnormalities, history of prematurity, recent respiratory infection, and obesity (57, 58, 61–63).

In summary, many children with OSAS can be identified as being at risk for postoperative respiratory problems on clinical grounds. Without polysomnography, the "otherwise healthy" child at risk for problems because of a high RDI may be missed. Although T&A is usually performed as an outpatient procedure, high-risk children require inpatient monitoring to assess the need for intervention if respiratory problems occur. These interventions may include repositioning, supplemental oxygen, placement of nasopharyngeal airways, continuous positive airway pressure (CPAP), or endotracheal intubation.

Predictors of Postoperative Persistence and Long-term Recurrence of OSAS

Although T&A is helpful in relieving OSAS in patients with adenotonsillar hypertrophy, children with severe disease may not be completely cured by surgery. Suen and coworkers (56) found baseline polysomnography to be the prime predictor of surgical success, as patients with an RDI < 19 were likely to have an RDI < 5 after surgery, while patients with an RDI > 19 were less likely to have such a good response. Patients with contributing factors for OSAS, such as obesity or cerebral palsy, are less likely to have complete resolution of OSAS after surgery.

Only one study has evaluated the long-term recurrence of childhood OSAS. Guilleminault and colleagues reevaluated adolescents who had been successfully treated during childhood by T&A (64). Of 49 potential cases, 31 could be located and 23 underwent polysomnography. Three patients (13% of those evaluated) were found to have OSAS. Interestingly,

these were all males. This study suggests that patients with childhood OSAS may be at risk for recurrence. One study suggested that patients with primary snoring do not generally go on to develop frank OSAS (65).

3. TO DEFINE AREAS IN WHICH FURTHER INVESTIGATION IS NEEDED TO DETERMINE NORMAL VALUES AND PREDICTORS OF MORBIDITY

As already summarized, case reports and small studies have clearly demonstrated that childhood OSAS can result in pulmonary hypertension, systemic hypertension, growth failure, excessive daytime sleepiness, behavioral problems, and impaired academic performance. However, the prevalence of these complications has not been established, and risk factors for complications of OSAS have not been defined. While risk factors for immediate postoperative complications have been defined, little is known about risk factors for recurrence of disease. The literature indicates that children who are younger, have severe OSAS, or have additional medical complications (such as cerebral palsy) are more likely to develop complications from OSAS. However, in the otherwise healthy child with OSAS associated with adenotonsillar hypertrophy, the predictive factors for morbidity are unknown. The current state of knowledge is hampered by the fact that many of the studies of childhood OSAS did not include polysomnography, and those that performed polysomnography did not always use standard pediatric criteria (11). Thus, further studies are required to determine which clinical and polysomnographic parameters are predictors of OSAS and complications thereof. In addition, further studies are required to establish definitive normative data on breathing during sleep.

4. TO DEVELOP AND ORGANIZE A MULTICENTER COMMITMENT TO OBTAIN THE REQUIRED DATA

The ultimate goal of the ATS workshop was to lay the groundwork for future, multicenter studies that would address the preceding issues. The theoretical, methodological, economic, and ethical issues concerned in collecting data in large numbers, which would be generalizable to the general population, were discussed. While the inherent difficulties of coordination in methodology, data collection, data retrieval, data analysis, and quality control of multicenter trials are formidable, it was felt that this approach offers the best opportunity to obtain sufficient data to address these issues. Careful design and implementation of such trials will be required. Some points are highlighted below.

Study Design

There was unanimous agreement among the pediatric sleep specialists present that a randomized, controlled trial involving an untreated control limb would be unethical in groups in which there was a clear consensus that treatment is needed (i.e., patients with moderate to severe OSAS). This was based on the irrefutable evidence that, if untreated, severe OSAS can result in serious morbidity and even death (66-68). However, because little is known regarding the natural history, morbidity, and relative risks of treatment in patients with mild OSAS, a randomized, controlled trial would be both reasonable and desirable for this population (69). Cross-sectional studies and longitudinal observational studies are also feasible. Because most children are cured after tonsillectomy and adenoidectomy, valuable information can be obtained by evaluating patients before and after surgery. However, potential

confounding effects of surgery need to be taken into consideration.

Study Group

Questions include: In which population(s) is the need for data on outcomes identification the greatest, e.g., patients with upper airway resistance syndrome/mild OSAS, or those with more severe OSAS? Should the study group be confined to certain ages, or are comparisons across age groups feasible? Should initial studies be limited to children with OSAS secondary to adenotonsillar hypertrophy, or should children with obesity, craniofacial anomalies, or neuromuscular disease be included? Strict eligibility criteria are needed in order to avoid selection bias. It will be important to control carefully for socioeconomic, ethnic, and cultural differences.

Polysomnographic Methods

A variety of techniques and equipment are available for collecting polysomnographic data (11). Strict standardization of polysomnography and scoring is essential. Attention must be paid to interobserver reliability and reproducibility of data. An issue to be resolved is whether measurement of esophageal pressure is useful and feasible for the clinical assessment of OSAS in children.

Techniques for Neuropsychological Assessment

One of the outcomes of central concern is the effect of OSAS on the neuropsychological functioning of the child. The literature to date remains inconclusive about the neurodevelopmental outcomes of sleep disruption in children. Studies that have examined adults with OSAS cannot necessarily be used to help us understand pediatric outcomes. In fact, adult studies offer limited information that could pertain to pediatric patients, owing to methodological problems such as selection bias, and potential problems of obtaining self-reports from children about their state of sleepiness. Perhaps most importantly, central nervous system effects of chronic hypoxemia and sleep fragmentation may be associated with different developmental outcomes. Neuropsychological outcomes in children represent the study of a developing nervous system. Thus, hypoxemia must be understood within a context of **neuropsychological** development.

Neuropsychological outcomes must be evaluated within a context of the constructs suspected to be affected by OSAS. In particular, constructs such as global intelligence, attention, memory, language, executive functions, **visuospatial/motor** processing, academic achievement, and psychosocial adjustment would be important to examine in a developmental outcome study. Perhaps the most important question that needs to be answered in the development of OSAS outcome studies is the age group of the children being examined. It would be desirable to study the age group in which childhood OSAS is most prevalent, i.e., 2-6 yr of age. In children younger than 4 yr of age, the aforementioned neuropsychological constructs are difficult to examine with standardized measures, although measurement of these constructs has become possible (e.g., NEPSY [70]). In children more than 4 yr old, it is more likely that these outcomes can be measured; in particular, outcomes that relate to academic performance and self-regulation behaviors (e.g., attention, impulse control), which may be associated with other comorbid conditions such as attention deficits. The use of different tests for different age groups may interfere with long-term follow-up.

Future studies will need to carefully consider several other issues in their design if they are to capture the neurodevelop-

mental outcomes associated with OSAS. Measures that may be sensitive to changes in sleep need to be included. Specifically, neuropsychological tests sensitive to disrupted sleep are those that can assess reaction time and track changes in performance over an extended timed interval. The time of day in which the neuropsychological tests are administered is also important to the design. Careful recording of the duration of symptoms, and documentation of subjective and objective sleep loss, may be important control variables.

SPECIFIC RESEARCH QUESTIONS

Many research questions remain unanswered. Examples are as follows.

Measurement

What are the normal ranges for the occurrence of obstructive apneas and hypopneas during sleep in children of different ages? How should hypopneas be measured and defined? What is the best method to quantitate upper airway resistance? What degree of paradoxical inward rib cage movement during inspiration, and what level of esophageal pressure, are normal in children of varying ages? How do these measures correlate with end tidal CO₂? What is the best index of arousal in children? Should the American Sleep Disorders Association criteria (6) be used to classify arousals, or should these criteria be modified? How important are subcortical arousals? What are the best methods for the evaluation of cardiovascular complications?

Outcomes

What level of apnea index/apnea hypopnea index is *clinically* significant in children? What are the clinical manifestations and prevalence of the upper airway resistance syndrome in children? What is the interaction between sleep architecture and OSAS in children? What is the prevalence of failure to thrive in children with OSAS? What are the risk factors for failure to thrive? What is the relation between OSAS, *neuropsychological* function, and behavior? What clinical and polysomnographic parameters are predictors of morbidity in children with OSAS? Are there subsets of children who are at greater risk for complications?

Natural History

What is the natural history of childhood OSAS? Is childhood OSAS a precursor of adult OSAS, or a separate disease process? What is the prevalence of recurrence during later life? What are the risk factors for recurrence? What are the long-term consequences of elevated nocturnal blood pressure and other autonomic changes in children with OSAS? What is the effect of obstructive apnea on craniofacial growth and structure? What role do genetic, ethnic, and anthropometric factors play in childhood OSAS?

Treatment Efficacy

Is tonsillectomy and adenoidectomy the best initial treatment for all children with OSAS? In what subsets of children are tonsillectomy and adenoidectomy less likely to be effective?

CONCLUSION

Many unanswered questions remain regarding childhood obstructive sleep apnea syndrome, and there is a dearth of large, well-controlled studies. Further endeavours will be made to develop collaborative projects to address these issues.

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