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Assessment of Sleep-Disordered Breathing in Pediatric Neuromuscular Diseases

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SUPPLEMENT ARTICLE

Assessment of Sleep-Disordered Breathing in Pediatric Neuromuscular Diseases

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ABSTRACT

This is a summary of the presentation on the assessment of sleep-disordered breathing in pediatric neuromuscular diseases, presented as part of the program on pulmonary management of pediatric patients with neuromuscular disorders at the 30th annual Carrell-Krusen Neuromuscular Symposium on February 20, 2008. *Pediatrics* 2009;123:S222–S225

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Abbreviations

OSA— obstructive sleep apnea
REM—rapid eye movement
SDB—sleep-disordered breathing
FEV_1—forced expiratory volume in 1 second
IVC—inspiratory vital capacity
MIP—maximal inspiratory pressure

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SLEEP-ASSOCIATED RESPIRATORY DISORDERS are a major cause of morbidity and mortality in children with neuromuscular disease. They have a prevalence of >40%,[1] a 10-fold greater occurrence than in the general population.[2] Gas-exchange abnormalities and disrupted sleep architecture may occur in >80% of patients with neuromuscular disease.[3] Neuromuscular weakness can result in 2 different types of nocturnal respiratory problems: obstructive sleep apnea (OSA) and nocturnal hypoventilation. Both will be defined here, and pathophysiology specific to neuromuscular disease will be reviewed. The challenges of diagnosis of these conditions and the tools available to evaluate their presence will be explored.

OBSTRUCTIVE SLEEP APNEA

OSA is defined as partial or complete upper airway obstruction during sleep, associated with at least 1 of the following: (1) sleep disruption; (2) hypoxemia; (3) hypercapnia; or (4) daytime symptoms.[4] On observation, there is continued chest and abdominal motion in the absence of airflow during sleep. In contrast to the common pathophysiologic mechanism of adenotonsillar hypertrophy contributing to OSA,[5] individuals with neuromuscular disease may also have weakness of the pharyngeal dilator muscles in the upper airway, which contribute to increased upper airway resistance during sleep because these muscles are required to maintain airway patency.[6] This becomes most evident in rapid eye movement (REM) sleep,[6] when these muscles are atonic. In addition, OSA may be compounded by the presence of obesity or upper airway abnormalities including retrognathia and macroglossia, which are also risk factors for OSA that contribute to a reduced airway diameter.

In neuromuscular disease, the presence of OSA often precedes the development of nocturnal hypoventilation. One retrospective study that studied the presentation of sleep-disordered breathing (SDB) in Duchenne muscular dystrophy evaluated 34 subjects, of whom 32 had polysomnography; 64% had symptoms of SDB, including daytime lethargy, headache or somnolence, and/or nighttime snoring or sleep disturbance. Interestingly, the presence or absence of symptoms did not predict SDB.[7] In addition, the presence of OSA was detected in this group during the first decade of life, as compared with nocturnal hypoventilation, which appeared in the second decade.

NOCTURNAL HYPOVENTILATION

In all individuals, there is a relative hypoventilation that occurs during sleep as a result of blunting of the hypoxic and hypercapnic drive to breathe. Therefore, there is a 25% reduction in tidal volume, a rise in arterial partial pressure of carbon dioxide of 3 to 4 mm Hg, and a reduction in arterial partial pressure of oxygen of similar magnitude.[8] In neuromuscular disease, this is exacerbated by weakness of the inspiratory muscles, with consequent "underbreathing" that further impairs gas exchange.[9] This also first manifests in REM sleep because of muscle hypotonia.[6] Furthermore, the presence of kyphoscoliosis can restrict lung capacity and, therefore, contributes to an impairment of ventilation.[9]

Initially, compensation for hypoventilation occurs with an arousal response that prevents prolonged oxygen desaturation or hypercapnia.[10] Unfortunately, it is at the expense of a good night's sleep, with sleep fragmentation resulting in daytime fatigue and hypersomnolence. With time and progression of disease, the ventilatory chemosensitivity is reset, and the arousal response becomes blunted, allowing longer periods of REM sleep, during which alveolar hypoventilation occurs.[10] Eventually, respiratory drive becomes depressed, and severe hypoventilation then becomes present during both day and night. Respiratory failure is the major cause of death in this population.[10]

Being a continuum, defining what constitutes clinically significant nocturnal hypoventilation is not straightforward. Although all definitions include the presence of hypercapnia and some degree of oxygen desaturation, specifics vary according to group and patient age. An adult consensus conference published in *Chest* in 1999 defined nocturnal hypoventilation as symptoms plus the presence of either an arterial carbon dioxide level of >60 mm Hg or >5 minutes asleep spent with oxygen saturation at <88%.[11] This definition was split by the International Classification of Sleep Disorders, published in 2007, into 2 categories: sleep-induced hypoventilation and sleep-induced hypoxemia.[12] The former was defined as a rise in arterial carbon dioxide of >45 mm Hg or "disproportionately increased relative to levels during wakefulness."[12] Sleep-induced hypoxemia was defined as oxygen desaturation to <90% for at least 5 minutes with a nadir of at least 85% or >30% of total sleep time with oxygen saturation at <90%. In children, the definition is more complicated, and there has been no clear consensus on a definition.

CONSEQUENCES OF UNTREATED SDB

Both OSA and nocturnal hypoventilation are associated with significant morbidity and mortality rates. The neurobehavioral consequences of disrupted sleep are well documented, including a profound impact on cognitive function.[13,14] Pulmonary hypertension can result from vasomotor recruitment of the pulmonary circulation in response to hypoxemia and hypercapnia.[15] SDB also has significant impact on growth. Failure to thrive can result from impaired insulin-like growth factor 1 and growth-hormone release.[16–18] These effects are largely reversible with treatment of SDB. A significant impact on quality of life has also been demonstrated with treatment.[19,20]

ASSESSMENT OF SDB

There are a variety of tests that can be performed to predict the presence of SDB, with varying degrees of utility. The ideal marker should be one that can be used in a clinical setting as a part of routine assessment of the patient with a neuromuscular disorder. To a great extent, this remains elusive. Alternatively, nocturnal tests can be used to screen for the presence of SDB. Polysomnography, or formal sleep study, remains the gold standard for diagnosis but is not widely available.

Daytime Tests

Daytime symptoms of SDB, especially hypoventilation, are vague and may be attributable to other facets of neuromuscular disease. They may include morning lethargy and headaches, anorexia, and poor growth.[10] Although in severe cases clinical features are evident, many patients with slower disease progression develop symptoms insidiously.[10] As a result, the symptoms are often only appreciated once they are corrected with treatment.

In a prospective study of 60 adults and children with various neuromuscular diseases, all were evaluated for SDB. The majority of subjects had symptoms of SDB, including disturbed sleep, snoring, and restless legs.[1] Despite the high prevalence of moderate-to-severe SDB (42%), symptoms were not predictive of its presence.

Similarly, clinical signs of SDB are difficult to recognize. Although snoring and obstructed breathing may be suggestive of OSA,[21,22] hypoventilation and apneas may be more difficult to detect.

Physical examination may yield some clues to the presence of SDB, although findings are not specific for this condition. The presence of adenotonsillar hypertrophy, mouth breathing, nasal obstruction, and hyponasal speech may suggest the presence of OSA. Cor pulmonale and digital clubbing may be present in severe disease. Most often, however, physical examination will be noncontributory. Clinical diagnosis correlates poorly with polysomnography and is correct for only 30% to 56% of patients.[23]

Questionnaires aimed at diagnosis of OSA in the pediatric population have been developed but are indeterminate in almost half of those queried.[24,25] In addition, parents are often unable to predict the severity of OSA on the basis of their observations.[26] It is likely even more difficult to predict hypoventilation given the vague symptoms and clinical signs.

Pulmonary function tests likely are the best clinical predictors of nocturnal hypoventilation. Hukins and Hillman[27] conducted a prospective study of 19 subjects over the age of 12 years with Duchenne muscular dystrophy. A forced expiratory volume in 1 second (FEV_1) below 40% predicted was sensitive for the presence of SDB (91%) but not specific. An FEV_1 below 20% predicted is associated with daytime carbon dioxide retention.

In another prospective study, predictive thresholds were determined for different degrees of nocturnal hypoventilation.[28] Hypoventilation confined to REM sleep was predicted by an inspiratory vital capacity (IVC) at <60% and maximal inspiratory pressure (MIP) at <45 cm H_2O. Hypoventilation continuously through the night, regardless of sleep stage, was predicted by IVC at <40% predicted and MIP at <40 cm H_2O. Finally, diurnal respiratory failure was predicted by IVC at <25% predicted and MIP at <35 cm H_2O. The IVC is a surrogate measure of forced vital capacity, which in a small prospective series of children with congenital and limb girdle muscular dystrophies was predictive for nocturnal hypoventilation at <40% predicted, with a high sensitivity and specificity.[29]

Measurement of daytime capillary or arterial blood gases can reliably predict nocturnal hypoventilation if arterial carbon dioxide is at >45 mm Hg on a daytime sample.[27] Some would argue, however, that when evidence of daytime hypercapnia is present, nocturnal hypoventilation is almost certainly present, and an opportunity to intervene at an earlier point when findings were limited to nocturnal events may have been missed.

Nocturnal Tests

Polysomnography, or formal sleep study, remains the gold standard for assessment of SDB.[4,23] It is the only technique that involves comprehensive noninvasive

monitoring of both cardiorespiratory function and sleep. It involves continuous monitoring by a sleep technologist of electroencephalogram, electromyogram, chest and abdominal movement, airflow, oxygen saturation, and carbon dioxide level, as well as video. In addition to SDB, it can also be used to differentiate seizures, periodic limb movements, and other parasomnias. Importantly, there is no significant variability in respiratory parameters from night to night, making it a robust test for the assessment of SDB.[30] It has some drawbacks, however, in that it is an expensive and labor-intensive test that is not readily available in all centers, and there may be long wait times to obtain a study. It is also disruptive for families, and the monitoring may interfere with normal sleep, in particular limiting REM sleep, during which SDB will first manifest.

Given the limitations of polysomnography, the search for a simpler and less involved method of screening for SDB has been ongoing. Homemade audiotapes and videotapes lack sensitivity or specificity for diagnosis.[31,32] Studies conducted during naps of a few hours' duration are unlikely to contain REM, particularly when conducted in an unfamiliar environment. They therefore have low sensitivity, and they run the risk of underestimating the severity of SDB.[33]

Overnight oximetry is a more widely available test that can be performed overnight in a patient's home in a noninvasive manner. Patterns of desaturation on oximetry may be suggestive of SDB. Repetitive clusters of "saw-tooth" desaturation may occur in REM sleep in the presence of OSA, whereas prolonged periods of desaturation may be evident with hypoventilation.[10] In a cross-sectional study of 349 "healthy" children referred to a sleep laboratory for possible OSA, Brouillette et al[34] found that although oximetry has a positive predictive value of 97%, the severity of SDB was not discernible. Oximetry also did not distinguish between hypoventilation and OSA, an important consideration for guiding treatment. Furthermore, a "normal" pulse oximetry reading did not rule out SDB, because respiratory events that resulted in arousals rather than desaturation were not detected. In addition, technical problems including motion artifact and a long built-in averaging time of the device can result in overestimation or underestimation of respiratory events.

The addition of capnography to oximetry has been proposed as an additional tool to aid in the diagnosis of SDB, but it has not been evaluated rigorously. In 1 adult case series of nocturnal oximetry and capnography, all of those who had hypercapnia also showed evidence of desaturation.[35] No comparison was made to polysomnography. In pediatric patients, a retrospective review by Kirk et al[36] of 609 pediatric polysomnographies was intended to show good agreement between end-tidal and transcutaneous carbon dioxide monitoring and did, but the authors also found that 12% of the subjects with a low apnea-hypopnea index had abnormally high carbon dioxide levels, which were clinically significant. The role of capnography, therefore, is not entirely clear but may be a helpful adjunct to overnight oximetry.

More sophisticated forms of ambulatory testing have been proposed for overnight assessment of SDB, largely specifically investigating OSA. Only those that replicate most of the sleep laboratory assessment have been successful.[37–42] It is important to realize, however, that with the exception of a single pilot study of patients with Duchenne muscular dystrophy,[43] they have not been evaluated for the purpose of detecting hypoventilation. There are several new technologies emerging, however, that may be able to serve this need.

CONCLUSIONS

The diagnosis of SDB remains challenging. It is a common problem, with insidious onset of symptoms. With the exception of pulmonary function tests (FEV_1 or forced vital capacity of <40% predicted or IVC of <60% predicted), there currently are no reliable clinical indices that can be evaluated during the day to predict SDB. Polysomnography remains the gold standard for diagnosis of SDB. Other nocturnal tests may be helpful for screening. Establishment of a diagnosis of SDB is important, however, given its significant impact on morbidity and mortality and its amenability to treatment. A high index of suspicion for SDB, therefore, is required by those caring for children with neuromuscular disease and risk of SDB.

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