Sleep Issues in Pediatric Neuromuscular Disorders

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Introduction

Sleep-related breathing disorders (SRBD) are defined as recurrent, partial, or complete cessation in breathing that disrupts normal sleep and ventilation. These include central apnea, hypoventilation, and the spectrum of obstructive sleep apnea (OSA) attributable to wide array of disorders from simple snoring to complete upper airway closure. Moreover, they are very common in children with neuromuscular disorders (NMD) that can be hereditary or nonhereditary in origin. The prevalence of SRBD in NMD is greater than 40%, i.e., 10 times more than general pediatric population, and suggests the involvement of respiratory muscles. It's quite a challenge in recognition and diagnosis of SRBD, as they are overlooked, unrecognized, or misdiagnosed.

Children with NMD are more prone to hypercapnic hypoventilation and hypoxemia. The adverse pathophysiological changes resulting from NMD compromise ventilatory mechanism and development of hypoxemic conditions that include pulmonary artery hypertension, cor-pulmonale, and neurocognitive dysfunction. The ensuing complications from deranged ventilatory mechanisms in NMD can be further aggravated and fastened with underlying OSAS. The coexistent illnesses contribute for more decreased chemical neuroresponsiveness when compared to children with either disorder alone. Hence, it warrants early recognition and addressing of SRBD and OSAS in children with NMD. If left untreated are likely to contribute greater morbidity, mortality and sleep-related hypoxemic complications when left untreated.

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Pediatric Neuromuscular disorders

The most important executive function of sleep is breathing. The diaphragm is the principle muscle for inspiration during wakefulness and sleep.

Respiratory Physiology in Sleep

During stages of REM (Rapid Eye Movement) and NREM (Non-Rapid Eye Movement), there is a decreased sensitivity of respiratory center to chemical and mechanical inputs along with a major decrease in the stimulant effects of cortical inputs. Likewise, upper airway resistance increases during sleep compared to wakefulness, thereby aggravating upper airway occlusion and obstructive sleep apnea syndrome (OSAS) in susceptible individuals. The hypoventilation during sleep is attributable for reduction in oxygen consumption and carbon dioxide production when compared to wakefulness.

In REM sleep, respirations become faster and more irregular. The respiratory frequency persists through hypoxia, hypercapnia, and metabolic alkalosis, suggestive of neurogenic forces superseding chemotactic reflexes during REM sleep. The sensitivity of respiratory muscles to respiratory center outputs is also reduced and more marked in REM sleep. The elemental feature in REM sleep respiratory physiology is that diaphragm assumes all functions of respiration. During REM sleep, there is marked atonia of all muscles (tongue, pharyngeal, laryngeal, intercostal muscles, etc.) of the body except oculomotor muscles and with major incapacitance for any significant function. In addition, there appears to be supraspinal inhibition of γ-motor neurons (and to a lesser extent α-motor neurons) and presynaptic inhibition of afferent terminals from muscle spindles. The diaphragm, being driven almost entirely by α-motor neurons and with far fewer spindles than intercostal muscles, has little tonic (postural) activity and therefore escapes reduction of this drive during REM sleep. This helps to explain the increase in abdominal contribution to breathing in REM sleep.

In NREM, sensitivity of diaphragm to respiratory center output is more when compared to accessory muscles and along with notable breathing that is regular both in amplitude and frequency.

In sleep, ventilatory drive in response to hypoxia and hypercapnia is also reduced. In NREM, there is a decrease in minute ventilation, largely due to a rise in end-tidal carbon dioxide tension ($PETCO_2$).

Neuromuscular disorders are broad distinct diseases that involve nerves, muscles, or their connections. Likewise, these disorders may share common features of reduced diaphragmatic strength, weakness of upper airway dilators, or cardiomyopathy that contributes to the development of SRBD. The diaphragmatic weakness in children with NMD is primarily responsible and detrimental for ventilatory compromise. It is markedly evident in REM sleep, at a time when diaphragm is the only effective respiratory pump. NMD patients with diaphragmatic weakness rely on intercostal and accessory respiratory muscles to breathe; when these muscles

become atonic in REM sleep, they are prone to hypoventilation. Thus, predisposing children with NMD to hypercapnic hypoventilation and first evidenced during REM sleep. Hence, two different types of sleep-associated nocturnal respiratory disorders are seen in children with neuromuscular weakness:

1. Obstructive sleep Apnea
2. Nocturnal hypoventilation

Sleep-related central hypoventilation is the primary pattern of SRBD in children with Duchenne Muscular Dystrophy (DMD), Spinal Muscular Atrophy (SMA), congenital myotonic dystrophy, limb-girdle muscular dystrophies, and childhood-onset maltase acid deficiency (see Table 7.2). Likewise, children with myotonic dystrophy, congenital muscular dystrophy, congenital non-progressive myopathies, spinal muscular atrophy, and myasthenia gravis exhibit sleep-related chronic obstructive hypoventilation because of a combination pharyngeal muscle weakness, predisposing to upper airway collapse, chest and abdominal wall weakness.

Sleep-Related Clinical Manifestations in NMD

SRBD are common in children with NMD, occur irrespective to the pathogenesis of each of these disorders, and manifest especially during REM sleep. These symptoms can be detected even when muscle weakness is still mild and even with no evidence of diurnal respiratory dysfunction. Labanowski et al., in a prospective study of 60 neuromuscular patients demonstrated disturbed sleep, snoring and restless legs in a majority of them (both adult and pediatric).

The children present with diverse symptoms and are isolated which include nocturnal restlessness, frequent unexplained awakenings and with awakenings gasping for air, snoring of variable loudness along with lapses in respiratory activity, difficulty waking up in morning and with prolonged sleep inertia. During daytime, there is excessive somnolence, fatigue, and inappropriate napping that lead to failure to thrive in the infant and poor school grades in the child. In addition, changes in mood, attention deficit, and learning difficulties are also observed. In severe cases, patients exhibit nocturnal cyanosis, intractable insomnia, morning lethargy, early morning headaches, nausea, vomiting, and hypoxia-induced nocturnal seizures. Polycythemia, hypertension, and signs of heart failure can also be seen. Sitting positions at night, nocturnal cyanosis, severe morning lethargy, headaches, and vomiting indicate advanced neuromuscular impediment to ventilation in sleep.

Likewise, sleep-related clinical symptoms result from hypoventilation and become more prominent and severe with progression of disease. Children with sleep-related ventilatory deficits exhibit continuous nocturnal hypoxemia or triggering episodes of oxygen desaturation that can precipitate restlessness, arousals, and sleep fragmentation.

Nevertheless, symptoms are poorly predictive of SRBD in children with NMD. It is even more difficult in children with low intellectual functioning. They can be

minimal despite significant apneas and severe nocturnal oxygen desaturations. Likewise, some report symptoms suggesting nocturnal hypoventilation, but these may be misinterpreted as part of the progressive deterioration of the underlying neuromuscular disorder.

Diagnostic and Clinical Evaluation of SRBD

Respiratory insufficiency in children with NMD is an early indicator for a progressive disease. Moreover, impairment of respiratory muscles occurs in various NMD and in some they are progressive to non-ambulatory stage. According to the International Classification of Sleep Disorders (ICSD)-3 (2014), neurological disorders for causation of SRBD are diagnosed distinctly and are included in clinical division of sleep-related breathing disorders and cited under sleep-related hypoventilation due to a medical disorder (see Table 7.1). Here the "medical disorder" is comprehensive and includes lung parenchymal or airway disease, pulmonary vascular pathology, chest wall disorder, neurologic disorder such as neuromuscular disorders (disorders of brain, spinal cord, or phrenic nerve), and myopathies. The current ICSD-3 criteria for sleep-related hypoventilation in pediatric age group is in synonymous with hypoventilation, as defined in AASM scoring manual: Hypoventilation is scored when the arterial PCO_2 (or surrogate) is >50 mmHg for >25% of total sleep time. The surrogates of arterial PCo_2 are end-tidal PCO_2 or transcutaneous PCO_2 (diagnostic study) or transcutaneous PCO_2 (titration study).

Clinical History

A focused clinical history and certain components of physical examination on background of ongoing NMD can aid in evaluating sleep-related breathing disorders.

The patient should be evaluated for craniofacial abnormalities such as micrognathia, dental malocclusion, high arched palate, etc., as they are commonly observed in NMD and compromise oropharyngeal lumen. Likewise, anatomical changes in the oropharyngeal region including tonsillar hypertrophy and macroglossia (sometimes seen in hypothyroidism or acromegaly) may also be present in

Table 7.1 ICSD-3 criteria: Sleep-related hypoventilation due to a medical disorder

1. Sleep-related hypoventilation is present
2. A lung parenchymal or airway disease, pulmonary vascular pathology, chest wall disorder, neurologic disorder, or muscular weakness is believed to be the primary cause of hypoventilation
3. Hypoventilation is not primarily due to obesity hypoventilation syndrome, medication use or a known congenital central alveolar hypoventilation syndrome

patients with neuromuscular disease. Kyphoscoliosis that is commonly observed in patients with NMD inhibits chest and abdominal movement, as postural alteration of the spine in conjunction with NMD-related weakness causes dysfunction of diaphragm and intercostal muscles, thereby translating into a less-efficient respiratory mechanism.

The presence of weak cough reflexes, obesity, restrictive pulmonary disease, medication effects, and malnutrition should be ruled out as these exacerbate SRBD in children with NMD.

Predictors for SRBD in Children with NMD

The principal effect with impairment of respiratory muscles in NMD is compromise of ventilatory mechanisms. Serial monitoring of pulmonary functioning tests, in children with NMD, once they are capable to participate in testing (>5 years) may aid in predicting which NMD patients are more likely to have sleep-related hypoventilation. Likewise, it assists in affirming rather than concluding SRBD merely basing on symptoms. Sleep-related central hypoventilation can likely be present in a child with NMD when inspiratory vital capacity falls below 40% of predicted or 60% of predicted in obese children, concomitant lung disease or during lung infection and a daytime $paCO_2$ level of >40 mmHg. Mellies et al. have found that IVC <40% of predicted had a 96% sensitivity and 88% specificity and daytime $paCO_2$ level >40 mmHg had a 92% sensitivity and 72% specificity in predicting sleep-related hypoventilation in children with NMD.

Assessment of SRBD

There are various clinically available tests to assess SRBD and with varying utility. The appropriate test that can be administered in an ideal clinical setting remains inconclusive. The gold standard method to document hypoventilation is by determining arterial partial pressure of carbon dioxide ($PaCO_2$) through processing of an arterial blood sample. However, limited by difficulty of drawing blood in sleep, 2007 AASM scoring manual states finding an elevated $PaCO_2$ obtained immediately after waking would provide evidence of hypoventilation during sleep. Nonetheless the elusiveness of recording sleeping $PaCO_2$, the ability to draw or process an arterial blood gas sample is rarely available in sleep centers.

Diurnal Tests

The diurnal clinical symptoms, evaluation and assessment tools yield some clues in early recognition of SRBD in children with NMD. These can be contributory as well as can be non-contributory in diagnosing SRBD.

The diurnal symptoms including morning headaches, lethargy, and daytime sleepiness are evident with either rapid or slower progression of NMD. The majority of diurnal symptoms in Labanowski et al. study of 60 adult and pediatric patients with various NMD were fatigue (83%), exertional dyspnea (78%), daytime sleepiness (63%), and morning headaches (45%). In addition, mean Epworth Sleepiness Scale score (ESS) in this study population was 7.5. Despite high reporting of SRBD in the study, symptoms along with ESS were not predictive of its occurrence.

Pediatric sleep-related questionnaires that are used to investigate or evaluate sleep issues in children remain inconclusive in majority cases including evaluation of OSA.

At the same time, it is challenging for parents in administering these questionnaires for:

1. Limited understanding on hypoventilation based on elusive symptomatology and signs of SRBD in a progressive NMD.
2. The limitation in predicting and assessing severity of SRBD based on these manifestations is always uncertain.

Pulmonary function tests are valuable in investigating and monitoring of response to treatment in patients with sleep-related respiratory problems. Hukins and Hillman in their prospective study of 19 patients with DMD have established forced expiratory volume in 1 s (FEV_1) < 40% and 20% than predicted was sensitive for presence of SRBD and daytime retention of Co_2, respectively.

Diurnal Polysomnography (PSG)

Polysomnography or formal sleep study remains the gold-standard test in diagnosing SRBD. Several studies have investigated the utility and reliability of daytime nap polysomnography (DPSG) versus nocturnal polysomnography (NPSG) in diagnosing SRBD. They have found DPSG is not as sensitive as NPSG in identifying SRBD. On the other hand, they tend to underestimate the severity of SRBD when compared to NPSG.

The measurement of PCo_2 reflects the effectiveness of alveolar ventilation and its measurement by sampling either capillary or arterial blood can estimate hypoventilation. The daytime capillary or arterial blood $PCo_2 > 45$ arguably suggest for nocturnal hypoventilation and reasoning for an early intervention and evaluation.

Nocturnal Tests

Polysomnography (PSG)

A comprehensive overnight PSG is the gold-standard test for assessing SRBD in children with NMD. The study involves a continuous non-invasive monitoring and

assessments are ascertained based on observational recordings from video, electroencephalogram (EEG), electromyogram (EMG), oxygen saturation and carbon dioxide level as well as chest and abdominal wall movements. The cohesive assessment helps in evaluation of cardiorespiratory compromise in association with sleep and altered sleep architecture (Reduced sleep time + Sleep efficiency), apart from differentiating seizures, periodic limb movements, and other parasomnias.

Katz et al. in their prospective study demonstrated that a series of single night PSG, was a valid measure and was without significant night to night variations in respiratory parameters. In addition, the study establishes clinical utility and predictability of PSG as a diagnostic tool in SRBD. The practice parameters from American Academy of sleep medicine indicate PSG in patients with neuromuscular disorders, manifesting sleep-related clinical symptoms with unequivocal and no plausible clinical explanation. The overnight PSG should be performed:

1. As early as possible in all neuromuscular patients for a baseline recording of respiratory parameters and repeated depending on course of the neuromuscular disease.
2. Regularly after initiation of treatment for assessment of treatment efficacy.

However, the test is limited for needing specialist centers and along with long wait times in scheduling and reimbursements. Likewise, it is expensive, labor intensive and might be disruptive for families. Moreover, there is a likely interference from monitoring with sleep, limiting REM during which SRBD manifests.

Overnight Oximetry

It is a non-invasive test and more widely available as it can be performed in a patient's home. Brouillette et al. has suggested a positive nocturnal oximetry trend graph has at least a 97% positive predictive value in child suspected of having OSA. Walsh et al. has demonstrated the reduction in requirement of formal PSG by 70% with use of domiciliary overnight oximetry.

The events of repetitive clusters of "saw tooth" desaturation may occur in children with OSA during REM sleep and prolonged periods of desaturation are observed with hypoventilation. The test has its own limitations: (1) It fails to interpret severity of SRBD as it hastens for early initiation of medical management. (2) Normal pulse oximetry cannot rule out the presence of SRBD as respiratory events attributed to arousals rather from desaturations are not detected. (3) The technical problems like motion artifact and as well as long built-in averaging time of the device can result either in overestimation or underestimation of respiratory events.

The search for simpler and other sophisticated ambulatory testing in assessment of SRBD has been ongoing. Home-made audio and video recordings lack sensitivity and specificity to diagnose SRBD. Kirk et al. study has demonstrated using capnography alone in diagnosing SRBD was not clear. The addition of capnography to oximetry, probably as an adjunct tool in diagnosing SRBD has been suggested.

However, the proposed role of capnography as an adjunct to oximetry in diagnosing SRBD warrants more studies.

Management of SRBD

Treatment

Over the years, advances in diagnosis and supportive care as such in ventilatory support or rehabilitative therapies have substantially improved functional status and survival in NMD children with SRBD.

The management of respiratory insufficiency during sleep is quite a challenge for: (1) It requires appropriate therapeutic intervention directed in augmenting the underlying disorder. (2) The applicable pharmacological therapies and time in initiation of either non-invasive or invasive ventilation is unclear.

There are different patterns of SRBD like apnea, obstructive apneas, hypopneas, central apneas, and frank central hypoventilation in children with NMD. For an optimal treatment, it is highly suggested for differentiating various apneas at diagnostic workup. The most common form of sleep-disordered breathing is hypoventilation and as such oxygen therapy alone is not only mostly ineffective, but may even be harmful, worsening the severity of CO_2 retention. Nowadays, non-invasive ventilation (NIV) has become a standard of treatment for an effective improvement in blood gases and reducing need for invasive ventilation. Ward et al. in their randomized control trial demonstrated beneficial effects of long-term non-invasive ventilation in patients with nocturnal hypoventilation and daytime normocapnia. Likewise, Piper and Sullivan study has demonstrated the importance of long-term nocturnal NIV in reducing severity of nocturnal hypoventilation.

The initial approach to treat SRBD in children with NMD is application of non-invasive positive pressure ventilation (NIPPV) during sleep. It has been effective in treatment of SRBD and hypoventilation in Duchenne muscular dystrophy (DMD) and various NMD. It is usually recommended:

1. Respiratory insufficiency unravels underlying NMD.
2. Chronic daytime respiratory failure.
3. Sleep-related hypoventilation is believed to be resulting from muscular weakness or NMD.

Non-invasive Positive Pressure Ventilation (NIPPV)

NIPPV is delivery of mechanical ventilation by augmenting alveolar ventilation and creating a transpulmonary pressure gradient without need for an indwelling artificial airway. The goals of NIPPV are firstly to improve gas exchanges by improving tidal volumes (VT) and secondly to decrease work of respiratory muscle. Likewise,

it can contribute in resetting chemosensitivity of respiratory center. There is no clear consensus in recommending long-term mechanical ventilation in cases of severe progressive neuromuscular disorders, as pros and cons of such are debatable. Even in such patients, NIPPV offers a meaningful hope of modality in maintaining reasonable alveolar ventilation without tracheostomy. Hence, NIPPV is attributable for improved quality of sleep, daytime sleepiness, quality of life, with an overall improvement in respiratory distress index and increasing longevity. The modes of delivery of NIPPV are bi-level positive airway pressure ventilation (BiPAP), volume-cycled ventilation, and continuous positive airway pressure (CPAP).

BiPAP is not as efficacious as volume-cycled ventilation when given through mask. Furthermore, BiPAP devices generate maximum inspiratory pressure of 30 cm H_2O resulting in low delivery of VT when compared to volume-cycled ventilation. Conversely, BiPAP ventilatory support is less complicated to initiate and less costly. BiPAP or volume-cycled ventilation can be considered in clinical situations where hypoxemia completely or in part results from hypoventilation. The role of CPAP as a first-line treatment in children with NMD warrants more studies. However, CPAP may be beneficial in children with suspected obstructive sleep apnea in absence of hypoventilation. For most NMD and predominantly children with DMD, CPAP remains ineffective as thoracoabdominal impairment is principal cause for sleep-related respiratory disturbances.

The optimal positive pressures required to reduce obstructive sleep apneas or hypopneas and stabilize ventilation should be determined either in sleep laboratory or by careful bedside monitoring and observation. After application of NIPPV, it is essential for a close bedside assessment of its effectiveness by the respiratory care team, including the physician. Furthermore, children treated with NIPPV must be observed by qualified professional staff using cardiac and respiratory monitors, pulse oximetry, and blood gases as and when necessary.

The complications commonly encountered with delivery of NIPPV include injury to face secondary to mask, eye irritation, conjunctivitis, skin necrosis/ulceration, gastric distension, and emesis into facial mask. The eye irritation can be minimized with use of appropriate fitting equipment and clear occlusive dressing. Similarly, skin necrosis/ulceration can be minimized either with use of a properly fitting mask or by use of a patch or skin dressing applied to skin pressure point. The other uncommon serious complications that need to be vigilant are for aspiration and pneumothorax.

Invasive Mechanical Ventilation

The increased respiratory exertion resulting either from progression of NMD as such or secondary to superimposed infections furthers for more stabilization of ventilation and may even necessitate for invasive ventilation. The consensus on indication for invasive ventilation is subjective. Conversely, it is critical as part of supportive care in children with advanced NMD and compromised respiratory

status. The common indications for need of mechanical ventilation: (1) Upper airway compromise resulting from weakness of facial, oropharyngeal, and laryngeal muscles impedes secretion clearance and swallowing. Consequently, placing the patient at risk for aspiration and causing mechanical obstruction of the upper airway. (2) The weakness of inspiratory muscles compromising expansion of lung by causing microatelectasis, ventilation/perfusion mismatch and with resultant hypoxemia. Likewise, weakness of expiratory muscles causes ineffective cough and secretion clearance and with increased risk for aspiration and pneumonia. (3) The acute complications of illnesses like pneumonia or pulmonary embolism may worsen the already compromised respiratory system.

It is essential to be watchful for complications as they can occur at any period of invasive mechanical ventilation and some are life threatening. A few which include: (1) ventilator-induced lung injury (2) Barotrauma and volutrauma, and (3) Ventilator-Associated Pneumonia (VAP).

However, it is well established that NIV is much superior to invasive mechanical ventilation in patients with NMD needing long-term ventilatory support. NIV takes precedence for (1) Very economical and with ease of administration. (2) Less burden on caregivers. (3) Greater portability (4) Potential reduction and elimination of airway complications (5) Reduced need for hospitalization.

Interfaces

The modality of NIPPV involves delivery of pressurized gas to lungs through a mask or mouthpiece that is affixed to the nose, mouth, or both. The clinically relevant issue is to select an appropriate interface with due consideration for patient comfort and minimal leakage. Moreover, selection of a larger nasal mask in view of patient comfort has adverse clinical effects:

1. The need for extreme pressures to secure mask would result in dermal abrasion around margins of mask.
2. The larger masks in children enclosing both oral and nasal passages with intent to minimize leaks contribute for an increased risk for aspiration pneumonia, gastric distension with air, feeding difficulties, and worsening of gastro-esophageal reflux.

In children needing long-term NIPPV, nasal mask interface would be an ideal choice either to maintain or to regulate required peak inspiratory pressures. The nasal-oral masks can be used safely in children provided there is reasonable level of monitoring. In acute settings, nasal-oral mask is superior to nasal masks in reducing oral leaks. The initial experiences with newly available interfaces, providing NIPPV in children like helmet device, nasal pillows or plugs and modified wide-bore soft nasal tubing systems are promising. However, experiences with these devices are preliminary, warranting more studies.

Home Mechanical Ventilation

The institution of home mechanical ventilation (HMV) has shown to prolong and improve quality of life in children with NMD. The number of children on home mechanical ventilation is reported to be increasing and has been well accepted as a standard treatment in children with chronic respiratory failure. HMV is favorable in children developing progressive respiratory failure or intractable failure to wean mechanical ventilation. Besides, HMV can also be helpful in children with increased respiratory load from airway or lung pathologies, ventilatory muscle weakness, and failure of neurologic control of ventilation. However, lack of studies limits consensus on guidelines of institution of HMV.

Special Disorders

Duchenne Muscular Dystrophy (DMD)

DMD is X-linked form of muscular dystrophy characterized by a defect in gene that affects synthesis of dystrophin protein. The clinical symptoms manifest between 3 and 4 years of age and with gradual deterioration in muscle function. With the gradual progression, children become less ambulant and wheel chair dependent before their adolescence. However, steroids have been effective in prolonging ambulation and improving respiratory muscle strength and clinical outcome. Likewise, ambulation, extent, and rate of progression of weakness in respiratory muscles causing respiratory insufficiency, daytime and nocturnal gas exchange impairment can aid in assessing clinical outcome and longevity.

The SRBD associated with DMD is more common in REM sleep and is demonstrated with significant drop in minute ventilation when compared to NREM. The impaired ventilator drive is a possible mechanism in these patients. There is a bimodal presentation of SRBD, with manifestation of OSA in first decade and hypoventilation more commonly at the beginning of the second decade. Their initial presentation is very subtle to notice and include continuing increasing numbers of nocturnal awakenings, daytime somnolence, fatigue, and morning headaches. In addition, these patients are at more risk of developing upper airway obstruction.

The aforesaid complaints when reported by patients should especially be drawn attention for a thorough evaluation by a physician. However, there are no clear guidelines for timing of polysomnography in patients with DMD. As such one study has correlated sleep hypoventilation with an awake $PaCo_2$ of >45 mmHg and a base excess >4 mmol/L. In another study, sleep study alone in home has demonstrated SRBD in children with SRBD.

The treatment of SRBD in Duchenne's muscular dystrophy with non invasive ventilation.

Spinal Muscular Atrophy (SMA)

SMA is a disorder that affects motor neurons of spinal cord and brain stem, thereby causing weakness of muscle and atrophy. The types of SMA in children are as listed in Table 7.2. It is the second most common NMD in children with an incidence of 8 per 100,000 live births.

SRBD is common in all forms of SMA and along with alterations in sleep architecture. The children presenting with sleep problems, daytime somnolence, morning headaches, and attention deficit during daytime necessitates for a thorough evaluation. The other most common and serious complication of SMA that can cause insidious onset of sleep hypoventilation is restrictive lung disease.

Table 7.2 Major neuromuscular disorders in children and along with type of SRBD

Neuromuscular disease	Mode of inheritance	Gene location	Type of SRBD
1. Duchenne muscular dystrophy (DMD)	XLR	Xp21	Hypoventilation, OSA
2. Becker muscular dystrophy	XLR	Xp21	Hypoventilation, OSA
3. Limb-girdle muscular dystrophy (LGMD)			
(a) LGMD1A	AD	5q22-q34	Hypoventilation
(b) LGMD2B	AR	2p13-2p16	
(c) LGMD2C	AR	13q12	
(d) LGMD2A	AR	15q15.1	
(e) LGMD2D	AR	17q12-q21.33	
4. Facioscapulohumeral muscular dystrophy			Hypoventilation, OSA
5. Emery-Dreifuss	AD	4q35 deletion	Hypoventilation
6. Congenital muscular dystrophies	XLR	Xq28,	OSA, hypoventilation
7. Myotonic dystrophy	AR	6q, 9q31-q33, unknown.	CA, OSA, hypoventilation
8. Spinal muscular atrophy	AD	19q13.2	
(a) Type I (Werdnig–Hoffman disease)	AR	5q11-5q13.	OSA, hypoventilation
(b) Type II (intermediate severity)	AR		
(c) Type III (Kugelberg–Welander disease)	AD, AR.		
9. Congenital Myasthenic syndrome	Unknown		Hypoventilation
10. Congenital myopathies	Unknown		OSA, hypoventilation

AD autosomal dominant, *AR* autosomal recessive, *XLR* X-linked recessive, *CA* central apnea, *OSA* obstructive sleep apnea

Mellies et al. in their study have demonstrated that NIV was an effective long-term treatment of hypoventilation during sleep and respiratory failure. Non-invasive ventilation during sleep eliminates SDB and normalizes sleep architecture in these children. Conversely, ideal settings for commencing NIV have not been clearly established. In some children, the decision to start NIV in prolonging survival may pose ethical conundrum. Even in such cases where NIV cannot prolong survival, it may aid in alleviating symptoms and allowing child to be cared at home.

Limb-Girdle Muscular Dystrophy (LGMD)

LGMD is a broad term for group of disorders causing weakness and wasting of girdle musculature. They are highly heterogeneous both clinically and genetically. The various types of LGMD are as listed in Table 7.2. The various forms of LGMD have childhood onset and may have severe progression resembling DMD. The type of SRBD noted in these children is similar to children with DMD.

Myotonic Dystrophy (MD)

Myotonic dystrophy is most common autosomal dominant disorder affecting children and adults. It is multi-organ disease affecting the muscles, brain, heart, gastrointestinal tract, lens, and reproductive organs. The incidence is 1:8000 births. SRBD has been reported up to 34% of patients with MD.

The children manifest extreme daytime somnolence, sleep fragmentation and these may even present before weakening of respiratory muscles. Similarly, learning disabilities may be noted in childhood-onset myotonic dystrophy type-1 disorder. In addition to respiratory-related arousals, it has been found that about a 1/3 of children has evidence of periodic limb movement during sleep, leading to sleep fragmentation.

Conclusion

The NMD are heterogeneous and have detrimental effects on respiratory function and sleep. Besides, progressive muscle weakness compromises function of upper respiratory system, cough, and clearance of secretions. Nonetheless, initial manifestations of sleep-related symptoms resulting from NMD are very subtle. The severity of SRBD-related symptoms depends on the distribution, rate of progression, and form of neuromuscular defects. Any alarming SRBD-related manifestations warrant for regular assessment of respiratory function during wakefulness and sleep in these patients. As such hypoxemia and hypoventilation are common during sleep; the timely initiation of clinical interventions may improve the quality of life and diminish the high morbidity and mortality associated with NMD.

Key Points

1. Sleep-related breathing disorder in children can present with diverse symptoms and are isolated which include nocturnal restlessness, frequent unexplained awakenings and with awakenings gasping for air, snoring with variable loudness along with lapses in respiratory activity, difficulty waking up in morning and with prolonged sleep inertia.
2. Children with sleep-related ventilatory deficits exhibit continuous nocturnal hypoxemia or triggering episodes of oxygen desaturation that can precipitate restlessness, arousals, and sleep fragmentation.
3. Positive oximetry testing has a high positive predictive value in identifying sleep apnea in children. The oximetry graph shows a typical saw tooth pattern.
4. Sleep-related breathing disorder is common in all forms of spinal muscular atrophy along with alterations in sleep architecture.
5. The sleep-related breathing disorder associated with Duchenne muscular dystrophy is more common in REM sleep and is demonstrated with significant drop in minute ventilation when compared to NREM.
6. In children needing long-term NIPPV, nasal mask interface would be an ideal choice either to maintain or to regulate required peak inspiratory pressures.

Suggested Reading

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