

Original Articles

Sleep-disordered Breathing in Children with Duchenne Muscular Dystrophy

TK WONG, TNH LEUNG, BWY YOUNG

Abstract

Advances in Paediatric Polysomnography have led to increased recognition of sleep-disordered breathing in children suffering from Duchenne muscular dystrophy (DMD). Because of the unique physiological alterations during sleep, respiratory muscle dysfunction in DMD may be recognised during sleep early in the disease. Recognised patterns include: 1) hypoxaemia; 2) obstructive apnoea, central apnoea, and hypopnoea. These may have important contribution to development of progressive cardiorespiratory failure. Early diagnosis with nocturnal polysomnography is the most conclusive way to assess nocturnal respiratory insufficiency in DMD children. Potential use of non-invasive ventilatory support should be discussed with patient and care takers early in the disease.

Key words

Duchenne muscular dystrophy; Sleep-disordered breathing; Polysomnography

Introduction

Duchenne muscular dystrophy (DMD) is the most common type of muscular dystrophy, with an incidence estimated at 1 in 3500 male births.¹ Despite recognition of the gene 16 years ago,² little has been achieved on human application of gene therapy, cell therapy, as well as pharmacological therapy.^{3,4} Majority of DMD patients passed away between the age of 15 and 25 years, with cardio-respiratory cause as the leading cause of death.⁵

Advances in polysomnography in children in the past 2 decades have led to a significant progress in recognition of various breathing problems during sleep. This has often been collectively referred to as Sleep-disordered breathing (SDB).

The pathophysiology and implication of SDB in DMD patients is not fully elucidated yet. Most reports are limited to cohorts of a few patients. Nevertheless, it is now becoming clear that SDB can be detected early in the disease in otherwise asymptomatic DMD children. Furthermore, these may have important contribution in the development of progressive cardiorespiratory failure.

SDB in Children with DMD

Respiratory muscle dysfunction in DMD patients may first be noted during respiratory illness or exercise. However, it may occur during sleep at an even earlier stage of disease and is less likely to be recognised. Recognised SDB in DMD patients includes: 1) hypoxaemia; and 2) obstructive and central apnoea, and hypopnoea.

Hypoxaemia during sleep has been well documented in DMD patients. Mild intermittent hypoventilation associated with mild desaturation has been demonstrated in earlier study on 5 non-ambulatory adolescents.⁶ This finding has been confirmed with several studies.⁶⁻¹³

Significant SDB, in the form of frequent apnoeas and hypopnoeas has been reported in a cohort of 14 DMD patients, with mean age of 18.3 years, mean vital capacity of 1.24L who had no sleep-related symptoms and normal

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daytime blood gas. The mean apnoea hypopnoea index (AHI) was 9.6 ± 1 (mean \pm SD) event/hour, as compared to apnoea index of <1 event/hour in normal children. Significant periodic arterial oxygen desaturation associated with episodes of hypopnoeas were detected.¹⁰ Furthermore, regardless of the possible causes, sequential studies did show that hypoxaemia became more frequent and severe with age in DMD children.⁸

In contrast, the arterial carbon dioxide tension does not rise until the very terminal phase of the disease. Study on non-DMD patients with diaphragmatic paralysis has shown marked hypoventilation with oxygen desaturation and elevated arterial carbon dioxide (PaCO_2) in REM sleep.¹⁴ In DMD patients, decreased minute ventilation without increase in PaCO_2 has been demonstrated. It was proposed that this may be due to a lower metabolic CO_2 production related to reduction in muscle mass.¹⁵

Pathophysiology

DMD patients are prone to respiratory disturbances during sleep because of the unique physiological alterations during sleep, especially during rapid eye movement (REM) sleep.

Two important physiological changes occur during sleep. Both of them have potential significant impact on respiratory physiology in DMD patients.

1) Atonia of Intercostal Muscles and Accessory Muscles

While awake, breathing in DMD patients with muscular weakness is accomplished by combined effort of accessory muscles and diaphragm, while abdominal muscles support and serve as a fulcrum for the diaphragm. They can only increase minute ventilation by raising their respiratory rate. They also adopt a breathing strategy of alternating between using the diaphragm and then the other inspiratory muscles.¹⁶

During REM sleep, the combined effect of muscle atonia and diaphragmatic compromise will put DMD patients at risk of hypo-ventilation and oxygen desaturation.

a) During REM sleep, accessory muscle activity and cyclic inspiratory-related muscle activity of intercostal muscle disappear. Under this condition, the diaphragm is basically the only active respiratory muscle. Even in normal subjects, diaphragm activity is decreased and exhibits intermittent decremental activity during single

breaths and clustered pauses. As a result, there is a decrease in tidal volume, alveolar ventilation, mild decrease in oxygen saturation, and mild increase in PaCO_2 .

b) Diaphragmatic function in DMD patient is compromised in 3 aspects: i) increased chest wall compliance related to intercostal muscle weakness; ii) mechanical disadvantage due to horizontal placement of diaphragm in children with neuromuscular disease;¹⁷ iii) fatty tissue infiltration and fibrosis in DMD patients with advanced disease.¹⁸

Whether diaphragmatic weakness has a major contributing role in the early REM desaturation is still unclear.¹⁹ Measuring transdiaphragmatic pressure during sleep may help clarify the issue. However, recruitment of the patients has proved difficult due to the invasive nature of the study.^{10,20}

2) Increased Upper Airway Resistance

During REM sleep, atonia of pharyngeal muscle will lead to increased upper airway resistance even in normal subjects. In DMD patients, it is even worse because of the preferential involvement of the pharyngeal muscles.¹² Macroglossia, which is present in about 1/3 of the DMD patients, may also increase the upper airway resistance.²¹ Like other children, they may also develop adenotonsillar hypertrophy, which increases the upper airway resistance even further.

Increased upper airway resistance during sleep is believed to be the major contributing factor in development of apnoeas and hypopnoeas, early in the disease. In children without neuromuscular weakness, the increased upper airway resistance frequently manifests as obstructive apnoeas and hypopnoeas. However, in DMD patients, it often manifests as "central apnoea". This has been referred to as "pseudo-central apnoea". It reflects diaphragmatic fatigue, which manifests as inability of the weakened diaphragm to overcome the increased upper airway resistance.^{8,10,13}

The importance of upper airway resistance in development of early REM desaturation is supported by 3 important findings: 1) demonstration of reversal of "central apnoea" following treatment with continuous positive airway pressure;¹² 2) possible evolution with age of apnoeas from obstructive to apparently central in one study;⁸ 3) demonstration of normal respiratory drive in a group of advanced DMD patients, using the technique of occlusion pressure response.²²

Predictors of SDB in DMD

There has been a continual debate on when nocturnal polysomnogram is indicated. Several studies have looked into the predictors of sleep disordered breathing. These include daytime symptoms, pulmonary function indices, and daytime arterial blood gas tensions.

Daytime Symptoms

Studies on daytime symptoms, such as daytime hypersomnolence and headache, have yielded contradictory results. In earlier studies, no daytime complaint was documented in patients with advanced disease with SDB.¹⁰ Other researchers claimed that daytime symptoms were indeed present.²⁰ There may be 2 reasons for this discrepancy.

- 1) Sleep efficiency and sleep architecture are surprisingly preserved in the presence of significant nocturnal hypoxaemia.^{10,20} This is probably due to the fact that arousals from hypoxaemia in REM sleep are related to changes of intra-thoracic pressure generated by the contraction of diaphragm, which is lacking in the DMD patients. This preservation of sleep architecture explain the mildness or absence of daytime symptoms, because restorative non-REM sleep can still occur uninterrupted and in normal amounts.
- 2) Because of the subtle nature and the slow progression, symptoms may easily be overlooked.

Pulmonary Function Indices and Daytime Blood Gas Tensions

Studies have also shown that spirometry indices, Maximum Inspiratory Pressure (MIP), Maximum Expiratory Pressure (MEP), and daytime blood gas tensions have no significant correlation with nocturnal apnoea/hypopnoea and hypoxaemia.²³

The poor discriminating ability of pulmonary function testing for predicting respiratory muscle failure may be related to other factors such as upper-airway obstruction, ability to clear the airway, abdominal wall stability, obesity, malnutrition, and level of activity, which are all difficult to assess.

Diagnosis of SDB in DMD Patients

DMD patients at risk of developing respiratory dysfunction can be identified with the help of regular

pulmonary monitoring. This includes 6-monthly spirometry, respiratory muscle strength, and oxygen saturation. Despite their limitation in predicting nocturnal hypoxaemia, absolute vital capacity and daytime arterial CO₂ tension have been shown to have the strongest correlation with survival.²⁴ An absolute vital capacity of less than 1L has been considered as a reliable indicator of the onset of terminal phase of the illness.²⁴ Furthermore, a marked reduction in vital capacity of 20% or more when the patient assumes the supine position is strongly suggestive of diaphragmatic weakness.^{14,25}

Nocturnal polysomnogram (PSG) is considered the most conclusive way to assess nocturnal respiratory insufficiency. However, there are considerable controversies as to when PSG should be performed.^{8,12,24,26,27} The relative indications may include daytime symptoms, abnormalities of arterial blood gas, or observed obstructive apnoea.

Early PSG findings may include sleep disruption and paradoxical breathing in all stages of sleep, mild tachypnoea, and borderline oxygen saturation. If the study is normal, further testing is usually performed on a yearly basis or every 2 years unless there is an increase in symptoms, marked weight gain or loss, change in pulmonary function parameters, or increased hospitalisations for pneumonia.

Alternatively, nocturnal oximetry can be employed. Oximetry is particularly sensitive in DMD patients whose relative immobility reduces saturation trace artefacts and whose reduced pulmonary oxygen stores means that even small changes in total ventilation will result in detectable desaturation.

As the disease progresses, persistent nocturnal hypoventilation will ensue. The PSG will typically show a progressive worsening of apnoea and desaturation from involvement in REM sleep to both REM and non-REM sleep. Development of non-REM sleep abnormalities may signal impending respiratory failure and death.²⁸

Management of SDB in DMD Patients

The hypoxaemia is believed to be of pathological significance. It may lead to significant sleep disruption, resulting in daytime symptoms. In addition, it may also have significant contribution to deterioration of pulmonary function and development of cor pulmonale. Equally significant is the hypoxaemia associated with cardiac rhythm disturbances, which could predispose to early mortality.²⁹

However, because of the limited data available on the possible link between the specific SDB involved and the prognosis, there is no firm consensus yet on the type of intervention that should be used, which patients to treat, or at what stage of their illness to intervene.

Nevertheless, nocturnal non-invasive ventilation has been increasingly used in DMD patients.^{19,30-32} The indications may include: 1) nocturnal hypoxaemia; 2) sleep hypoventilation; 3) daytime hypercapnoea or dyspnoea.

The pros and cons of starting non-invasive ventilatory support should be considered.

- 1) Nocturnal non-invasive pressure support has been shown to be effective in treatment of apnoeas and hypopnoeas, together with reversal of oxygen desaturation.⁸ Reversal of significant hypoxaemia may prevent development of daytime symptoms, cor pulmonale, and sudden death.
- 2) Patients' perception of quantity and quality of life following treatment with non-invasive ventilation has been better than as expected previously.³³
- 3) There has been no direct link between the prognosis and detection of nocturnal hypoxaemia.
- 4) Pulmonary function continues to deteriorate (although at a slower rate) despite nocturnal pressure support and sustained reversal of daytime PaCO₂ abnormality.
- 5) Complication from non-invasive ventilation, like pressure sores, may be higher because of the muscle weakness, which impairs their ability to remove noxious stimuli.

Negative-pressure support devices such as the iron lung or cuirass ventilators are falling out of favour because of their low portability, and possible cause of obstructive apnoeas.³⁴ Nasal ventilation has become a popular and effective intervention for those patients requiring intermittent or nocturnal ventilation.

Considering the complex ethical issue, patients' expectation and perception of quality of life, and the limited understanding of the pathophysiology involved, it is highly recommended that the issue of ventilator support should be discussed with the patients and the care takers early in the disease.

Conclusion

SDB is increasingly recognised in DMD patients before the onset of terminal phase of their illness. Polysomnographic abnormalities include nocturnal hypoxaemia,

apnoea, and hypopnoea. Early detection is important since they might have important implications in the progression of the cardiopulmonary failure. Non-invasive ventilation is effective in reversal of the hypoxaemia, apnoea, and hypopnoea. However its use should be individualised with detailed discussion with the patients and parents.

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