Chapter 21
Sleep Breathing Disorders in Duchenne Muscular Dystrophy

Pnina Weiss

Case

An 18-year-old male with Duchenne muscular dystrophy (DMD) was admitted because of shortness of breath, cough, and a 20-lb weight loss over 4 months. He was diagnosed at age 5 years and became non-ambulatory at 10 years. At 13 years old, he developed cardiomyopathy and was put on enalapril and carvedilol; an implantable cardioverter defibrillator was placed. At 14 years of age, he underwent polysomnography (Figs. 21.1, 21.2, and Table 21.1) which documented obstructive sleep apnea (OSA); titration with bilevel positive airway pressure with spontaneous and timed mode (BPAP S/T) demonstrated optimal treatment with 12/4 cmH_2O and backup rate 20 breaths/min, which he used with variable adherence. His pulmonary function testing is shown in Table 21.2.

Two months prior to admission, he developed cough. He was diagnosed with bronchitis and given an antibiotic. He restarted airway clearance. He had nausea, decreased appetite, and abdominal pain. He stopped using his BPAP because of chest congestion and his oral medications because of nausea. He was seen in clinic; on exam he was uncomfortable, respiratory rate 28 breaths/min, heart rate 98 beats/min, blood pressure 72/45 mmHg, pulse oximetry (SpO_2) 92% on room air, and weight 62 kg. His exam was remarkable for coarse breath sounds. A chest radiograph is shown in Fig. 21.3. Arterial blood gas on room air showed pH 7.34, PCO_2 48 mmHg, PO_2 58 mmHg, and bicarbonate 28 meq/L. Cardiac echo demonstrated moderate dilation of the left ventricle with ejection fraction 18%

P. Weiss (✉)
Department of Pediatrics, Section of Respiratory, Allergy-Immunology and Sleep Medicine, Yale School of Medicine, New Haven, CT, USA
e-mail: pnina.weiss@yale.edu

C. Won (ed.), *Complex Sleep Breathing Disorders*,
https://doi.org/10.1007/978-3-030-57942-5_21

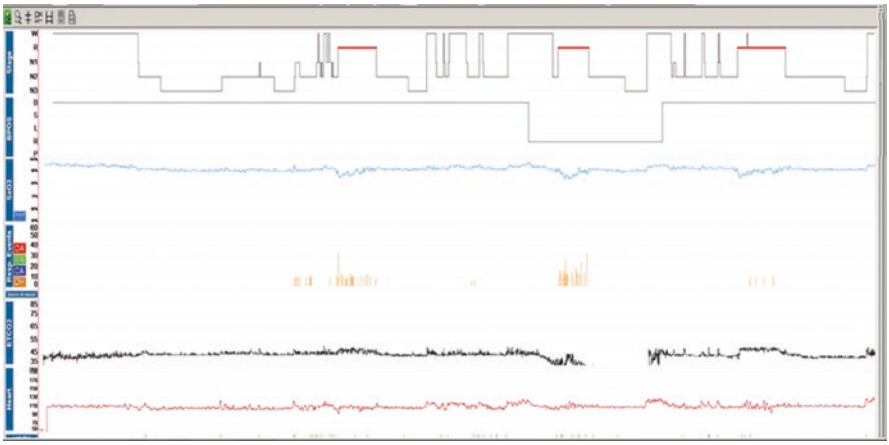

Fig. 21.1 Hypnogram of patient's PSG at age 14 years demonstrating OSA with hypoxemia during REM sleep. *PSG* polysomnography; *OSA* obstructive sleep apnea; *REM* rapid eye movement; *Stage* sleep stage (*W* wake, *R* REM, *N1* non-REM stage 1, *N2* non-REM stage 2, *N3* non-REM stage 3); *BPOS* body position (*B* back, *L* left, *R* right, *P* prone); SaO_2 arterial oxygen saturation via pulse oximetry; *Resp Events* (*OA* obstructive apnea, *MA* mixed apnea, *CA* central apnea, *OH* obstructive hypopnea); $ETCO_2$ end-tidal carbon dioxide; *Heart* heart rate

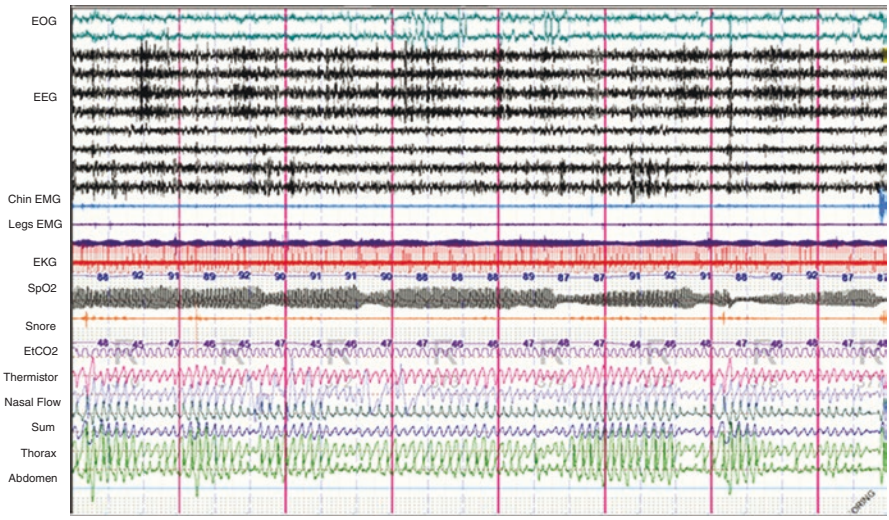

Fig. 21.2 Hypopneas with oxyhemoglobin desaturations and paradoxical respiratory effort during REM (4 min epoch) at age 14 years. *EOG* electrooculogram, *EEG* electroencephalogram, *EMG* eletromyogram, *EKG* electrocardiogram, SpO_2 pulse oximetry oxygen saturation, $EtCO_2$ end-tidal CO_2

Table 21.1 Polysomnographic report of this patient at age 14 years

TST (h)	6.2
Sleep efficiency (%)	76
Stage N1 (% TST)	4
Stage N2 (% TST)	55
Stage N3 (% TST)	23
Stage REM (% TST)	18
Obstructive AI (N/h)	0.2
REM obstructive AI (N/h)	0.9
AHI (N/h)	9.4
REM AHI (N/h)	39
Average SpO_2 awake (%)	96
Average SpO_2 asleep (%)	92
Nadir SpO_2 asleep (%)	84
Percentage time spent $SpO_2 < 90\%$ (% TST)	12
$EtCO_2$ awake (mmHg)	44
$EtCO_2$ asleep average (mmHg)	44
$EtCO_2$ asleep max (mmHg)	50
$EtCO_2 > 50$ mmHg (% TST)	0

TST total sleep time; *N1, N2, N3* Non-rapid eye movement sleep stages 1, 2, 3, respectively; *REM* rapid eye movement sleep; *AI* apnea index; *SpO_2* pulse oximetry oxygen saturation; *AHI* apnea-hypopnea index; *N* number; *$EtCO_2$* end-tidal carbon dioxide; *mmHg* millimeters of mercury

Table 21.2 Serial spirometric measurements on this patient

	3 years prior	3 months prior	This visit
FEV1 (% predicted)	29	16	15
FVC (L)	1.15	0.80	0.77
FVC (% predicted)	31	16	16
Peak cough flow (L/min)	130	120	80
MIP (cmH_2O)	−55	−45	−35
MIP (% predicted)	55	37	29
MEP (cmH_2O)	44	32	21
MEP (% predicted)	36	19	13

FEV1 forced expiration volume at 1 s, *FVC* forced vital capacity, *L* liters, *MIP* maximal inspiratory pressure, *MEP* maximal expiratory pressure

(decreased from his previous of 25% 3 months prior). He received intravenous fluid and was placed on supplemental oxygen. He became somnolent. His follow-up arterial blood gas on supplemental oxygen showed pH 7.13, PCO_2 78 mmHg, PO_2 120 mmHg, and bicarbonate 30 meq/L. He was put on BPAP S/T 12/4 cmH_2O with rate 20 breaths/min and 40% fraction of inspired oxygen (FiO_2). An arterial line was placed; follow-up arterial blood gas showed pH 7.40, PCO_2 41 mmHg,

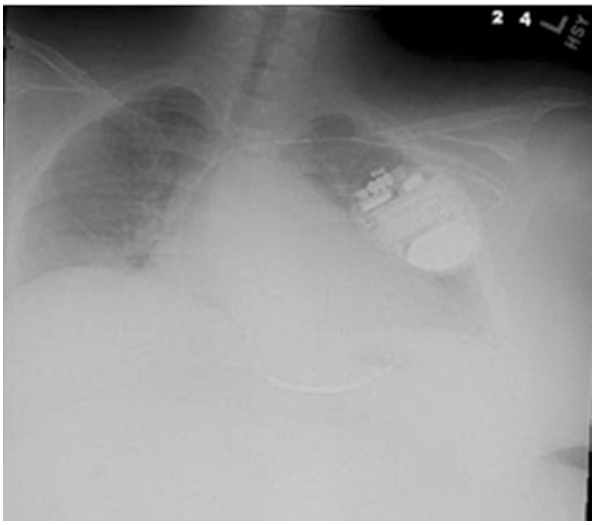

Fig. 21.3 Chest radiograph of the patient in the vignette

and PO_2 140 mmHg. He did well on BPAP S/T until he fell asleep, when he developed hypoxemia. Tidal volumes ranged 225–350 mL. Arterial blood gases showed worsening hypercapnia, which improved with increase in inspiratory positive airway pressure (IPAP) to 16 cmH_2O. Two nights later, he underwent polysomnography (PSG) which demonstrated optimal titration with average volume-assured pressure support IPAP 14–18 cmH_2O, expiratory positive airway pressure (EPAP) 4–6 cm H_2O, backup respiratory rate 22 breaths/min, and tidal volume 500 mL. He was discharged home after further stabilization of his cardiac medication regimen.

Discussion

This young adult has Duchenne muscular dystrophy with nocturnal hypoventilation and cardiomyopathy with congestive heart failure. DMD is an X-linked recessive disease affecting between 5600 and 7700 males in the United States, associated with mutations in the dystrophin gene [1, 2]. Dystrophin plays an important role in the stabilization of muscle fibers, and its loss results in degeneration of muscle fibers and muscle weakness. The onset of muscle weakness usually occurs between 2 and 3 years of age, first affecting proximal limb muscles and lower extremities. Children usually become non-ambulatory by age 12 years, as in the child in the vignette. Progressive respiratory muscle weakness resulting in respiratory failure and cardiomyopathy are the major causes of morbidity and mortality in these patients [1]. Mean survival was traditionally in late teenage years. However, mechanical ventilation, aggressive airway clearance, and glucocorticoid therapy have increased survival into the third decade [3].

Respiratory muscle weakness involving the chest wall and diaphragm results in restrictive lung disease with respiratory muscle fatigue, difficulty with airway clearance, mucus plugging, atelectasis, pneumonia, and respiratory failure. Management includes frequent monitoring of pulmonary function, lung volume recruitment, manual and mechanically assisted coughing, and nocturnal noninvasive ventilation (NIV), when indicated, with potential progression to daytime ventilation. These therapies decrease respiratory complications and improve quality of life and survival [4].

Sleep disordered breathing (SDB) is common in patients with DMD, usually progressing through four stages [5]:

- OSA without hypercapnia
- Hypoventilation, obstructive and/or central sleep apnea with hypoxemia, and/or hypercapnia during rapid eye movement (REM) sleep
- Hypoventilation, obstructive and/or central sleep apnea with hypoxemia, and/or hypercapnia during REM and non-rapid eye movement (NREM) sleep
- Daytime chronic respiratory failure

Polysomnographic evaluation with carbon dioxide (CO_2) level monitoring in children with DMD is necessary for early identification of SDB. OSA is the most common type of SDB, occurring in approximately 64% of patients and is correlated with increased body mass index (BMI) and corticosteroid use [5]. Children with DMD have increased upper airway resistance because of hypotonia of the upper airway, macroglossia, and a lower pulmonary functional residual capacity. Respiratory impairment is worse during REM sleep because during this stage of sleep, accessory respiratory muscles are paralyzed and the diaphragm becomes the primary functioning respiratory muscle. Meanwhile, the cephalad displacement of the diaphragm while recumbent reduces tidal volumes and ventilation. Children with DMD eventually develop diaphragmatic weakness associated with REM-related hypoxemia, which often worsens as pulmonary function deteriorates. REM latency has been noted to be longer in children with DMD and SDB, which may be due to sleep fragmentation from underlying SDB, or a compensatory mechanism to avoid REM sleep [6].

Hypoventilation can occur either with OSA or in isolation in children with DMD, particularly as the disease progresses. Hypoventilation in children is defined on PSG as >25% of the total sleep time with $CO_2 > 50$ mmHg. Nocturnal hypoventilation may result from an increased arousal threshold or a decrease in alveolar ventilation, respiratory muscle activity, ventilatory drive, pulmonary function, or a combination.

Central sleep apnea in association with OSA has also been reported, occurring primarily in older children with worse pulmonary function and more severe OSA [5]. Potential causes of central sleep apnea include hypoventilation, reduced hypoxic or hypercapnic ventilatory response, or increased loop gain and sleep stage instability. Cheyne-Stokes respiration has been described in patients with DMD and congestive cardiomyopathy [7]. Of note, chronic hypercapnia may actually attenuate the instability in breathing associated with cardiomyopathy by reducing the

controller gain and increasing the difference between the apneic threshold and the PCO_2. It is important to differentiate hypo- or normocapnic central events from hypercapnic central apneas that result from neuromuscular disease and respiratory muscle weakness [8]. Hypercapnic central apneas often occur during phasic REM, especially in the presence of diaphragm muscle weakness, with loss of excursion of both chest and abdominal signals.

Pulmonary function should be measured serially, starting at age 5–6 years. The best established measurements include forced vital capacity (FVC), forced expiration volume at 1 second (FEV1), peak expiratory flow rate (PEFR), and maximal inspiratory and expiratory pressures (MIP and MEP, respectively) [9]. In children with DMD, there is a maturational increase in FVC that reaches a peak (at the point at which their neuromuscular disease renders them non-ambulatory), plateaus, and then historically declines at a rate that was inversely proportional to the peak. Long-term corticosteroid therapy preserves pulmonary function, delaying the age at which the plateau in FVC occurs [10]. PSG with capnography should be considered in children with symptoms of SDB, especially because weight gain associated with glucocorticoid therapy may be a risk factor. In children who are unable to cooperate with spirometry, PSG may be considered to assess lung function.

An increase in respiratory support usually is necessary when children become non-ambulatory. Seated FVC, MIP, MEP, peak cough flow, and oxygen saturation should be measured at least every 6 months. Lung volume recruitment maneuvers are recommended when FVC decreases to 60% predicted or less, which can be performed with a self-inflated manual ventilation bag or mechanical insufflation-exsufflation device. Progressive scoliosis may require surgical intervention; guidelines addressing perioperative management have been published [11]. Preoperative PSG may be considered as an assessment of pulmonary function, if patients cannot cooperate with spirometry testing.

Further progression of disease is associated with weak cough, increasing the risk of complications such as atelectasis, aspiration, pneumonia, ventilation-perfusion mismatch, and respiratory failure, particularly during lower respiratory tract infections. Manual and mechanically assisted coughing should be initiated [4] when:

- FVC < 50% predicted
- Peak cough flow < 270 L/min
- MEP < 60 cm H_2O

For those who require assisted coughing, a home pulse oximeter is recommended.

Nocturnal assisted ventilation, preferably noninvasive, should be initiated as soon as there are symptoms of hypoventilation or SDB (e.g., fatigue, dyspnea, headaches, nocturnal awakenings, excessive daytime sleepiness, difficulty concentrating, frequent nightmares), regardless of pulmonary function. Because many children with DMD do not demonstrate symptoms of SDB, additional indications for nocturnal NIV include:

- FVC < 50% predicted
- MIP < 60 cm H_2O
- Awake SpO_2 < 95%
- Awake PCO_2 > 45 mmHg
- Abnormal sleep study

Nocturnal ventilation is also recommended for patients with abnormal sleep studies, which may include overnight oximetry, oximetry-capnography, or PSG with capnography. Sleep studies should be performed annually in those with symptoms of sleep disordered breathing since disease is progressive. Indications for nocturnal NIV based on PSG include:

- End-tidal CO_2 ($EtCO_2$) or transcutaneous CO_2 ($TcCO_2$) > 50 mmHg for >2% of the total sleep time
- Sleep-related increase in $EtCO_2$ or $TcCO_2$ > 10 mmHg over the awake baseline for >2% of total sleep time
- SpO_2 < 88% for >2% of total sleep time or for >5 min continuously
- Apnea-hypopnea index (AHI) > 5/h

Noninvasive ventilation with a backup respiratory rate, rather than continuous positive airway pressure, is preferred. A backup rate is often important as patients with DMD may have difficulty triggering breaths, particularly during REM sleep and/or as the disease worsens. Other strategies to assist with comfort and synchrony in neuromuscular disease include increasing the trigger and the cycle sensitivities, in order to allow the patient with weak respiratory effort to trigger and terminate assisted breaths appropriately. A prolonged inspiratory phase time with pressure support may be beneficial since these patients have issues with atelectasis and hypoxemia (in contrast to COPD patients on NIV, for example, who require long expiratory time to avoid air trapping). In the same manner, ventilator settings with higher peak flow and longer inspiratory time (Ti) may help optimize lung mechanics and provide a more comfortable ventilator experience for DMD patients.

The patient in the vignette met multiple criteria for initiation of NIV including decreased FVC, MEP, and peak cough along with abnormal PSG indices (SpO_2 and AHI); he was appropriately started on BPAP S/T. Serial PSG studies are recommended to follow respiratory support as overnight oximetry is not adequate to determine the adequacy of ventilation [12]. Unfortunately, the child in this vignette did not undergo subsequent PSGs until his admission. While he acutely required an increase in his ventilatory support because of pulmonary exacerbation with increasing atelectasis and congestive heart failure, he most likely needed a chronic increase in his IPAP and EPAP in order to treat his progressive restrictive disease.

Daytime NIV is indicated when, despite nocturnal NIV, a patient with DMD demonstrates:

- Awake SpO_2 < 95%
- Awake PCO_2 > 45 mmHg
- Dyspnea while awake

Noninvasive ventilation may be required during acute pulmonary exacerbations in patients with DMD. Hypoxemia is often due to hypoventilation or atelectasis; therefore, supplemental oxygen alone (as was used in this patient) often does not suffice and in some instances may worsen respiratory failure by blunting hypoxemic ventilatory response. BPAP S/T is often initially used in chronic hypercapnic respiratory failure. When disease is progressive, the best NIV modality may be volume-assured pressure support ventilation via a respiratory assist device (e.g., AVAPS™, iVAPS™) or via home ventilator (e.g., Trilogy™, LTV®). When patients lose the ability to use their upper extremities to self-apply or remove the mask interface, a ventilator (over a respiratory assist device) is recommended for its alarm and backup battery features.

Noninvasive ventilation in patients with DMD is associated with improved survival, gas exchange and sleep, and a reduction in hospitalizations, including to intensive care units [13, 14]. However, NIV does present some challenges. In children, chronic use can cause facial and nasal bridge flattening. If not carefully adjusted, patients may become dyssynchronous with their device (e.g., ineffective triggering, auto-triggering, and glottic closure) which can increase arousals, impair sleep quality, and result in decreased adherence. It is important in patients with neuromuscular disease, to ensure that the patient can effectively trigger ventilation. As previously mentioned, trigger/cycle sensitivities, peak flow, and inspiratory time should be carefully adjusted for patient comfort.

The potential adverse effects of using NIV in the context of cardiomyopathy with decreased ejection fraction merit consideration. Cardiomyopathy, with ensuing heart failure and arrhythmias, has emerged as a major determinant of survival in patients with DMD [15]. Early and consistent cardiac evaluation is recommended, especially in the late, non-ambulatory stage. Symptoms of heart failure may be difficult to detect in non-ambulatory patients with DMD. Fatigue, weight loss, vomiting, and abdominal pain may indicate worsening cardiac function, as was the case in the patient in the vignette. First-line therapy includes angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, which are often initiated even in asymptomatic patients with DMD as early as age 10 years [4]. Beta-adrenergic blockers are usually second-line therapy [16]. In an early randomized study of patients with DMD, NIV was instituted when FVC decreased below 50%; when compared to controls, there was quadruple the mortality rate in the treated group [17]. However, the study was later criticized as there was a higher prevalence of left ventricular dysfunction in those on NIV. So, while there is a potential for NIV to decrease cardiac output in patients with left ventricular dysfunction (by increasing intrathoracic pressure and decreasing left ventricular preload), at present, its use is not contraindicated in those who require it for respiratory support, especially if they are given cardioprotective medications. The argument for using NIV in patients with cardiomyopathy is that it has been shown to improve survival. It may be that with the potential adverse effects of respiratory insufficiency on cardiac function, earlier institution of NIV could have a cardioprotective effect [16].

It should also be noted that cardiomyopathy and heart failure in DMD has been associated with central sleep apnea with Cheyne-Stokes respiration. NIV

(especially without a backup rate) may exacerbate Cheyne-Stokes breathing by over-ventilating the patient and worsening loop gain. CSA related to Cheyne-Stokes breathing is often a hypocapnic phenomenon and occurs almost exclusively during NREM sleep, due to the dependence on PCO_2 and PO_2 on ventilatory control during this sleep stage. In contrast, CSA associated with neuromuscular disease has a very different pattern and mechanism from that seen with heart failure. Neuromuscular disease results in a hypercapnic central sleep apnea phenotype. In this case, central hypopneas and apneas emerge typically during REM sleep when respiratory muscle strength is at its weakest. For this type of central sleep apnea, NIV is the treatment of choice. Therefore, in a DMD patient with cardiomyopathy and CSA, careful attention has to be made at phenotyping the SDB (i.e., determine if it is hypocapnic CSA (driven by the cardiomyopathy) or hypercapnic CSA (driven by respiratory muscle weakness)). Treatment will differ depending on the CSA type, and the wrong therapy may actually worsen the sleep breathing disorder. Adaptive servo-ventilation (ASV) would be contraindicated in DMD patients because of both cardiomyopathy and neuromuscular disease.

Clinical Pearls

- Progressive respiratory muscle weakness resulting in respiratory failure and cardiomyopathy are major causes of morbidity and mortality in patients with Duchenne muscular dystrophy (DMD).
- Sleep disordered breathing in the form of OSA, hypoventilation, and CSA with and without Cheyne-Stokes respiration can be seen.
- OSA is the most common SDB, occurring in 64% of children treated with corticosteroids. Risk factors for OSA in patients with DMD include upper airway hypotonia, macroglossia, restrictive pulmonary disease, diaphragm muscle weakness, and obesity.
- Hypoventilation occurs due to respiratory muscle weakness. Patients may require noninvasive ventilation during sleep and, if severe, during the daytime. Special attention to features such as inspiratory time, flow rate, trigger, and cycle sensitivity should be made to optimize positive airway pressure or ventilator synchrony in DMD patients who may otherwise have difficulty triggering breaths or become dyssynchronous with the machine. In addition, a backup respiratory rate is always recommended due to this concern of poor breath triggering.
- Central sleep apnea with and without Cheyne-Stokes respiration can be seen in patients with DMD with cardiomyopathy. It is important to distinguish whether CSA is related to hypoventilation or high loop gain and heart failure, since each may be treated differently.
- Noninvasive ventilation in patients with DMD is associated with improved survival, gas exchange and sleep, and a reduction in hospitalizations, including to intensive care units. NIV is recommended in patients with DMD who require ventilatory support even in the presence of cardiomyopathy with low ejection fraction.

References

1. Finder J, Mayer OH, Sheehan D, Sawnani H, Abresch RT, Benditt J, Birnkrant DJ, Duong T, Henricson E, Kinnett K, McDonald CM, Connolly AM. Pulmonary endpoints in Duchenne muscular dystrophy. A workshop summary. Am J Respir Crit Care Med. 2017;196(4):512–9.
2. Nowak KJ, Davies KE. Duchenne muscular dystrophy and dystrophin: pathogenesis and opportunities for treatment. EMBO Rep. 2004;5(9):872–6.
3. Schram G, Fournier A, Leduc H, Dahdah N, Therien J, Vanasse M, Khairy P. All-cause mortality and cardiovascular outcomes with prophylactic steroid therapy in Duchenne muscular dystrophy. J Am Coll Cardiol. 2013;61(9):948–54.
4. Birnkrant DJ, Bushby K, Bann CM, Alman BA, Apkon SD, Blackwell A, Case LE, Cripe L, Hadjiyannakis S, Olson AK, Sheehan DW, Bolen J, Weber DR, Ward LM, Group DMDCCW. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. Lancet Neurol. 2018;17(4):347–61.
5. Sawnani H, Thampratankul L, Szczesniak RD, Fenchel MC, Simakajornboon N. Sleep disordered breathing in young boys with Duchenne muscular dystrophy. J Pediatr. 2015;166(3):640–645 e641.
6. Nozoe KT, Moreira GA, Tolino JR, Pradella-Hallinan M, Tufik S, Andersen ML. The sleep characteristics in symptomatic patients with Duchenne muscular dystrophy. Sleep Breath. 2015;19(3):1051–6.
7. Lemay J, Series F, Senechal M, Maranda B, Maltais F. Unusual respiratory manifestations in two young adults with Duchenne muscular dystrophy. Can Respir J. 2012;19(1):37–40.
8. Aboussouan LS, Mireles-Cabodevila E. Sleep-disordered breathing in neuromuscular disease: diagnostic and therapeutic challenges. Chest. 2017;152(4):880–92.
9. Meier T, Rummey C, Leinonen M, Spagnolo P, Mayer OH, Buyse GM, Group DS. Characterization of pulmonary function in 10-18 year old patients with Duchenne muscular dystrophy. Neuromuscul Disord. 2017;27(4):307–14.
10. Moxley RT 3rd, Pandya S, Ciafaloni E, Fox DJ, Campbell K. Change in natural history of Duchenne muscular dystrophy with long-term corticosteroid treatment: implications for management. J Child Neurol. 2010;25(9):1116–29.
11. Hull J, Aniapravan R, Chan E, Chatwin M, Forton J, Gallagher J, Gibson N, Gordon J, Hughes I, McCulloch R, Russell RR, Simonds A. British Thoracic Society guideline for respiratory management of children with neuromuscular weakness. Thorax. 2012;67(Suppl 1):i1–40.
12. Paiva R, Krivec U, Aubertin G, Cohen E, Clement A, Fauroux B. Carbon dioxide monitoring during long-term noninvasive respiratory support in children. Intensive Care Med. 2009;35(6):1068–74.
13. Ishikawa Y, Miura T, Ishikawa Y, Aoyagi T, Ogata H, Hamada S, Minami R. Duchenne muscular dystrophy: survival by cardio-respiratory interventions. Neuromuscul Disord. 2011;21(1):47–51.
14. Crescimanno G, Misuraca A, Purrazzella G, Greco F, Marrone O. Subjective sleep quality in stable neuromuscular patients under non-invasive ventilation. Sleep Med. 2014;15(10):1259–63.
15. Birnkrant DJ, Ararat E, Mhanna MJ. Cardiac phenotype determines survival in Duchenne muscular dystrophy. Pediatr Pulmonol. 2016;51(1):70–6.
16. McNally EM, Kaltman JR, Benson DW, Canter CE, Cripe LH, Duan D, Finder JD, Hoffman EP, Judge DP, Kertesz N, Kinnett K, Kirsch R, Metzger JM, Pearson GD, Rafael-Fortney JA, Raman SV, Spurney CF, Targum SL, Wagner KR, Markham LW. Contemporary cardiac issues in Duchenne muscular dystrophy. Circulation. 2015;131(18):1590–8.
17. Raphael JC, Chevret S, Chastang C, Bouvet F. Randomised trial of preventive nasal ventilation in Duchenne muscular dystrophy. French multicentre cooperative group on home mechanical ventilation assistance in Duchenne de Boulogne muscular dystrophy. Lancet. 1994;343(8913):1600–4.