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ORIGINAL ARTICLE

Sleep apnea in adult myotonic dystrophy patients who have no excessive daytime sleepiness

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Abstract
Purpose Sleep apnea is common in myotonic dystrophy (MD) and may cause respiratory failure. Most of the sleep studies have been performed in patients with excessive daytime sleepiness (EDS), which is a characteristic and strong predictor of sleep apnea. Therefore, we investigated the prevalence of sleep apnea in adult MD patients who have no EDS.
Materials and methods Epworth Sleepiness Scale was used to exclude EDS and a score over 10 was accepted as an indicator of EDS. Sleep studies of 17 adult MD patients with the Epworth sleepiness scale score ≤10 were retrospectively reviewed. Spirometry (n=16) and daytime arterial blood gasses were used to evaluate the relationship with nocturnal parameters.
Results On admission to the outpatient chest clinic, seven patients had normal spirometry, and ten had daytime hypercapnia and/or hypoxemia. All but one had sleep apnea (apnea–hypopnea index ≥5 events/h of sleep; mild in five, moderate in seven, and severe in four). Hypopneas were more common than apneas (16.9±13.2 events/h vs. 4.6±4.1events/h). Nocturnal desaturation episodes were very frequent (oxygen desaturation index, 19.7±20.3/h of sleep). Three patients had central sleep apnea and 13 had obstructive sleep apnea. Body mass index, spirometry parameters (FVC and FEV1) and arterial oxygen tension were moderately correlated with nocturnal oxygenation parameters. Apnea–hypopnea index showed moderate correlation with spirometry parameters (FVC and FEV1).
Conclusion Sleep apnea and oxygen desaturations are very common in MD patients who report no excessive daytime sleepiness. Daytime lung function parameters are not sufficiently reliable for screening sleep apnea. Therefore, we recommend routine polysomnography in MD patients.

Keywords Myotonic dystrophy · Excessive daytime sleepiness · Sleep apnea · Polysomnography

Introduction

Myotonic dystrophy (MD) is an inherited multisystem disorder, characterized by myotonia and weakness of the facial, jaw, and distal limb muscles. It is the most common form of muscular dystrophy in adults. Patients with MD are prone to various patterns of sleep-related breathing disorders (SRBD) including obstructive apneas and hypopneas, central apneas, nocturnal hypoxemia, and nocturnal hypoventilation [1–10]. All of these disorders may impact unfavorably on survival by causing pulmonary hypertension, cor pulmonale, and respiratory failure [9–12]. Respiratory-failure-related or sleep-related symptoms are not always typical in patients with neuromuscular diseases. These patients may have

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clinically significant SRBD in the absence of typical symptoms such as excessive daytime sleepiness, snoring, and apnea, and in the presence of normal daytime pulmonary functions. Therefore, early recognition and treatment of SRBD with nocturnal noninvasive mechanical ventilation at the right time is very important. However, polysomnography (PSG), which is a gold standard for SRBD, is not a routine investigation in patients with neuromuscular disease [10]. It is recommended if a patient with neuromuscular disease has symptoms suggesting SRBD, respiratory muscle weakness, abnormal daytime arterial blood gasses, or abnormal nocturnal oximetry [1,10].

Excessive daytime sleepiness (EDS) is a very strong predictor of sleep apnea. Therefore, PSG should always be considered in the presence of this symptom. EDS is common also in patients with MD [13–18]. Published sleep studies in MD patients with EDS have reported that sleep apnea is the most common cause of this symptom in MD [15,16,19,20]. However, the frequency of sleep apnea in MD patients who have no EDS is not known. Therefore, in this retrospective study, we aimed to investigate the prevalence of sleep apnea in adult MD patients who have no excessive daytime sleepiness (the Epworth Sleepiness Scale score ≤10). We also investigated the relationship between daytime pulmonary function parameters and sleep parameters.

Materials and methods

We retrospectively reviewed the medical records of adult MD patients, who were referred from the Division of Neuromuscular Diseases of Neurology Department for routine pulmonary evaluation. There were 24 patients with the diagnosis of adult MD. To exclude patients with EDS, we used the Epworth Sleepiness Scale (ESS), which is a standard questionnaire for the subjective assessment of daytime sleepiness [21]. Since the score "10" is considered the upper limit of normal, we accepted a score of >10 as an indicator of EDS. Of 24 adult MD patients, four were excluded (three with ESS score >10 and one with no ESS score). The remaining 20 patients with an ESS score ≤10 were accepted for the study but three of them declined to take part in the study because of absence of sleep study (n= 2) and hypothyroidism (n=1). Finally, 17 adult MD patients with an ESS score ≤10 were included in the study. A neurologist has assessed all patients and the diagnosis has been based on clinical presentation, myotonic discharges on electromyography, and genetic tests in some patients. Smoking habits, the presence of respiratory symptoms (dyspnea at rest or on exertion) and symptoms suggesting SRBD (snoring, apnea, daytime sleepiness, morning tiredness, frequent awakenings, and morning headache) on admission to the outpatient chest clinic, and the presence or absence of diaphragmatic elevation on chest X-ray were recorded from the medical files. As daytime pulmonary function evaluation, spirometry (forced vital capacity, FVC; forced expiratory volume in 1 second, FEV1; and FEV1/FVC ratio), and daytime arterial blood gasses, performed within 2 months of the relevant sleep study, were used in the study. Maximum inspiratory and expiratory pressures, which show respiratory muscle strength, were not included in the study because most of the patients had no acceptable measurements (failure to perform the measurements) or no measurements within 2 months of the sleep study. Flow-volume loops were also inspected for apparent upper airway obstruction (plateau or irregular abrupt changes in the loop).

PSG data of each patient were re-analyzed according to the American Academy of Sleep Medicine Manual for Scoring Sleep, 2007 by an experienced physician [22]. Apnea–hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of sleep, and oxygen desaturation index (ODI) as the number of oxygen desaturations of ≥3%/h of sleep. Sleep apnea was considered to be present if AHI was ≥5 events/h. AHI>15 events/h was considered clinically significant sleep apnea. Nadir pulse oxyhemoglobin saturation (SpO_2) less than 85% was considered pathological. Sleep-related hypoxemia was defined as "a SpO2 during sleep of <90% for more than five minutes with a nadir of at least 85%", or ">30% of total sleep time with a SpO2 of <90%" [23]. Daytime hypercapnia was defined as $PaCO_2$>45 mmHg and daytime hypoxemia as PaO_2<80 mmHg.

In our sleep laboratory, polysomnography comprising a four-channel electroencephalogram (central and occipital), two-channel electrooculogram, chin electromyogram, nasal canula, electrocardiogram, position sensor, chest and abdomen belts, limb movement sensors, microphone, and pulse oximetry is used. Sleep studies are performed without an oxygen supply. Sleep stages and respiratory parameters are scored manually. Sleep efficiency is derived as the ratio of total sleep time to total record time. An apnea is defined as a drop in the peak nasal canula excursion by ≥90% of baseline and the duration of the event lasts at least 10 s. A hypopnea is scored when the airflow reduced to ≤50% from the baseline associated with ≥3% drop in oxygen saturation and/or associated with arousal, lasting at least 10 seconds. An apnea is considered to be obstructive when respiratory effort is present and central when effort is absent.

Statistical analysis

Statistical analysis was carried out using SPSS 10.1. Data were expressed as mean±standard deviation. P<0.05 was considered as significant. Correlation between daytime pulmonary function parameters and nocturnal parameters were analyzed using the Spearman's rank correlation.

Results

Seventeen adult MD patients with an ESS score ≤10 were included in the study. There were four women and 13 men with a mean age of 42.2±10.9 (range 20–60)years. Four were current smokers, one was an ex-smoker, and the others were non-smokers. Their body mass index (BMI) ranged from 17 to 33 kg/m^2 (mean 24.7±4.1). All but two of them were ambulatory. No one had chest wall deformity. Cardiovascular state was stable in all. None had diaphragmatic elevation on chest X-ray. Of the 17 patients, eight (47%) had no respiratory symptoms and/or symptoms suggesting SRBD on admission to the outpatient chest clinic. In the remaining nine patients, the most frequent symptoms were dyspnea on exertion (n=7) and snoring (n=3). Other symptoms were apnea (n=2), daytime sleepiness (n=2), morning tiredness (n=2), frequent awakenings (n=1), and morning headache (n=1).

Daytime pulmonary function parameters

Sixteen patients had spirometry. Seven spirometries (44%) were normal (both FVC and FEV1 ≥80% of predicted), and the nine patients (56%) had an apparent restrictive ventilatory pattern (both FVC and FEV1 <60%). Significant upper airway obstruction was excluded in all patients with the inspection of flow-volume loops. Five patients (31.3%) presented with both normal spirometry and normal arterial blood gasses. Nine of 17 patients (52.9%) had daytime hypoxemia and eight (47%) had daytime hypercapnia. Overall, ten patients (58.8%) had daytime hypoxemia and/or hypercapnia on admission. Spirometry measurements and daytime arterial blood gasses of the patients are summarized in Table 1.

Both FVC and FEV1 were moderately correlated with $PaCO_2$ (R=−537, p=0.048 and R=−519, p=0.04, respectively), with PaO_2 (R=558, p=0.025 and R=554, p=0.026 respectively), and with daytime arterial oxygen saturation (R=641, p=0.008 and R=646, p=0.007, respectively).

Nocturnal oxygenation parameters

During sleep, eight patients (47%) had nadir SpO_2 less than <85% and the mean nadir SpO_2 of the group was 81.7%± 10.8% (53-94). Nocturnal desaturation episodes were very frequent (ODI, 19.7±20.3/h). ODI was over 10/h in eight patients. Desaturations were especially predominant during the rapid eye movement (REM) period of sleep (REM ODI: 28.2±26.8 vs. non-REM ODI: 16.8±18.7). Oxygen saturation was below 90% for a mean of 11.3%±21.4% of total sleep time. Nocturnal SpO_2 was always over 90% only in three patients. In the remaining 14 patients, SpO_2<90% was over 2% of total sleep time in seven patients (over 25% in four). Details of nocturnal oxygenation are shown in Table 2. Three patients had sleep-related hypoxemia (one with SpO_2 of <90% for 11.2 min with a nadir of at least 85% and two with >30% of total sleep time with SpO_2 of <90%).

Daytime PaO_2 was correlated with nadir SpO_2 (R=534, p=0.027), mean SpO_2 (R=593, p=0.012), and ODI (R=−571, p=0.017). Daytime $PaCO_2$ had no correlation with nocturnal oxygenation parameters. Both FVC and FEV1 showed correlation with ODI (R=−502, p=0.048 and R=−612, p=0.012, respectively). Among the clinical features, BMI was correlated with nadir SpO_2 (R=−650, p=0.005), with mean SpO_2 (R=−727, p=0.001), and with ODI (R=527, p=0.03). Dyspnea on exertion, which was the most common symptom on admission, did not show a correlation with nocturnal oxygenation parameters.

Table 1 Spirometry and arterial blood gas values in adult MD patients

Parameter	Value
FVC, %predicted (n=16)	68.6±18.9 (36–100)
FEV1, % predicted (n=16)	71.4±20.4 (35–102)
FEV1/FVC, % (n=16)	87.8±9.1 (71–100)
$PaCO_2$, mmHg (n=17)	45.5±5.9 (36–57)
PaO_2, mmHg (n=17)	78.1±9.8 (59–92)
HCO_3, mEq/L (n=17)	26.8±2.5 (23–31)
SaO_2, % (n=17)	94.6±2.3 (89–97)

Data presented are means ±SD; ranges indicated in parentheses.

Table 2 Polysomnographic data in 17 adult MD patients

Sleep efficiency, %	92.5±7.1 (78–100)
Sleep latency, minute	15.5±6.5 (5.5–29)
REM sleep, % of total sleep time	14.8±7.3 (1.4–25.8)
Mean SpO_2 during sleep, %	93.9±3.3 (85–97)
Nadir SpO_2 during sleep, %	81.7±10.8 (53–94)
SpO_2<90%, % of total sleep time	11.3±21.4 (0–79.2)
REM SpO_2, %	92.5±5.4 (77–98)
Non-REM SpO_2, %	94.2±3.0 (87–98)
ODI, per hour of sleep	19.7±20.3 (0.4–65.6)
REM ODI, per hour of REM	28.2±26.8 (0–77)
Non-REM ODI, per hour of NREM	16.8±18.7 (0.3–63.1)
AHI, events/ hour of sleep	21.5±14.5 (2.1–52.4)
Apnea index, events/h of sleep	4.6±4.1 (0.3–13.3)
Hypopnea index, events/h of sleep	16.9±13.2 (0.7–49.5)
REM AHI, events/h of REM	33.7±20.2 (2.9–78.7)
NonREM AHI, events/h of NREM	19.1±14.6 (2–53.1)

Data presented are means ±SD; ranges indicated in parentheses.

REM rapid eye movement, *SpO_2* pulse oxyhemoglobin saturation, *SpO_2<90%* percentage of total sleep time that SpO_2 was below 90%, *ODI* oxygen desaturation index, *AHI* apnea–hypopnea index

Sleep parameters

Polysomnographic evaluation showed that there was a predominance of light stages of sleep (stages I and II of non-REM sleep) in comparison to slow wave sleep (stages III of non-REM sleep; 62.0±11.4 % vs. 22.8±6.8%, respectively). Hypopneas were more common than apneas (hypopnea index, 16.9±13.2 events/h vs. apnea index: 4.6± 4.1 events/h). Hypopneas were predominant both in REM (hypopnea index, 28.7±19.3 vs. apnea index, 5.0±7.1, respectively) and non-REM (hypopnea index, 15.2±13.5 vs. apnea index, 4.4±4.2 respectively) sleep. The obstructive apnea index was 2.7±3.4 (0–12.9) and the central apnea index was 1.9±2.7 (0–9.1). All but one patient (93.3%) had sleep apnea (AHI≥5). AHI was between 5 and 15 in five patients (mild sleep apnea), between 16 and 30 in seven patients (moderate sleep apnea), and >30 in four patients (severe sleep apnea). Of 16 patients with sleep apnea, 68.8% (n=11) had clinically significant sleep apnea (AHI>15 events/h) and 36.4% of them had no dyspnea or sleep-related symptom. The single patient with AHI<5 had a daytime hypercapnia ($PaCO_2$=46 mmHg). The details of sleep parameters are in Table 2.

Of 16 patients with sleep apnea, only three (18.8%) had central sleep apnea. In patients with central sleep apnea, most of the central apneas occurred during the NREM period. Other 13 patients had obstructive sleep apneas. Of 13 patients with obstructive sleep apnea, seven had FVC <60% predicted, and eight had daytime hypoxemia and/or hypercapnia. Of 16 patients with sleep apnea, five (31.3%) had both normal spirometry and normal arterial blood gasses. Three patients with sleep apnea had additional diagnosis of sleep-related hypoxemia.

Both FVC and FEV1 were correlated moderately with AHI (R=−612, p=0.012 and R=−688, p=0.003, respectively), and the hypopnea index (R=−663, p=0.005 and R=−667, p=0.005, respectively). There was no correlation between arterial blood gasses and AHI.

AHI was correlated with nadir SpO_2 (R=−721, p=0.001), mean SpO_2 (R=−659, p=0.004), ODI (R=908, p=0.000), and SpO_2 <90% (R=630, p=0.007).

Discussion

The major findings of this retrospective study are: (1) sleep apnea and oxygen desaturations are very frequent in adult MD patients who have no excessive daytime sleepiness, (2) daytime hypercapnia and/or hypoxemia are common, and (3) daytime pulmonary function parameters and nocturnal parameters are not reliable for screening SRBD.

Sleep apnea in patients with neuromuscular diseases may cause daytime respiratory failure which increases morbidity and mortality, Therefore, early diagnosis and treatment of sleep apnea in these patients is very important. According to previous studies, the prevalence of sleep apnea in MD ranges between 15.8% and 75% but most of the patients included in these studies had EDS which is a classic symptom for sleep apnea [5,6,8,15,16,19,24]. In neuromuscular diseases, sleep apnea may be present in the absence of typical sleep-related symptoms such as EDS. Our retrospective study evaluated seventeen MD patients who had no EDS and found a very high rate of sleep apnea (93.3% with AHI >5 events/h) in this population. All but one patient had sleep apnea (five with mild, seven with moderate, and four with severe sleep apnea). Of patients with sleep apnea, 68.8% had clinically significant sleep apnea (AHI>15 events/h). Since the severity of sleep apnea may progress over time, it is important to know the patients with mild sleep apnea (AHI< 15 events/h). These patients with mild sleep apnea must be followed closely for the correct time of treatment.

The presence of symptoms for sleep apnea and nocturnal hypoventilation such as EDS, morning headaches, frequent arousals, fatigue, tiredness, or dyspnea is a recommendation for polysomnography in NMD [1,10]. Among these symptoms, EDS, which is a very characteristic symptom of sleep apnea, is very common in MD [13–18]. Guilleminault et al. found a correlation in MD patients between EDS and apnea index [3]. However, sleep apnea symptoms may be absent or be minimal despite significant apneas and severe nocturnal oxygen desaturations [25]. Some symptoms such as fatigue or tiredness may be misinterpreted as a part of the deterioration of the underlying NMD. Furthermore, symptoms of respiratory muscle weakness, especially dyspnea, may be absent or delayed due to reduced mobility related to peripheral muscle weakness. Although none of the patients in our study had EDS and 47% had no respiratory symptoms and symptoms suggesting SRBD, significant sleep apnea was very frequent. In this study, the most common symptom on admission was dyspnea on exertion, which is not a characteristic symptom for sleep apnea. Additionally, typical sleep apnea symptoms, such as snoring and apnea were rare.

There are a few studies which have evaluated the prevalence and the effect of hypoxemia during sleep in MD [5,6,8]. These studies showed that patients with MD are often hypoxemic during sleep and nadir oxygen saturation is correlated with BMI and daytime PaO_2. We, like others, found the same relationship. Additionally, we showed correlations of mean SpO_2, and ODI with both BMI and PaO_2. Among spirometry measurements, both FVC and FEV1 were related to ODI. Our study also showed a high correlation between AHI and ODI. These results support the use of overnight pulse oximetry as a screening test for SRBD in areas where PSG is not available. However, overnight oximetry may be insufficient in neuromuscular diseases as an arousal response can be triggered much before

a drop in SpO_2 of ≥3% is seen. Also, it may underestimate SRBD not associated with desaturations.

Because PSG is expensive and not universally available, daytime predictors of SRBD have been sought in various neuromuscular diseases [4,26–32]. However, relationships between nocturnal variables and daytime lung function parameters have been highly variable [1,4,31]. According to published literature on various neuromuscular diseases, patients with vital capacity less than 60% of predicted are likely to have SRBD [26,29]. Therefore, most specialists consider this value for recommending PSG in neuromuscular diseases. However, some factors like obesity, craniofacial abnormalities, and chest wall deformity increase the likelihood of detecting significant sleep apnea, even at higher lung function levels [33]. In our study, 43.8% of patients with sleep apnea had normal spirometry (two had BMI over 27). Overall, most of the studies in various NMD have shown less consistent and weaker relationships between nocturnal parameters and daytime lung function parameters [1,4,30,34]. Despite the high incidence of sleep apnea in MD, daytime predictors of SRBD were evaluated only in two studies [5,15]. One of them evaluated 25 patients who had at least one symptom suggestive of nocturnal hypoventilation [15]. The prevalence of SRBD has been reported as 36%. In that study, spirometry, maximal inspiratory and expiratory pressures, sniff nasal inspiratory pressure, and arterial blood gasses were used and none of them showed correlation with nocturnal parameters. The other study included 12 patients and evaluated sleep hypoxemia and its correlation with daytime pulmonary function [5]. In that study, only BMI and PaO_2 showed correlation with nadir SpO_2 and with the proportion of total sleep time with Sp02< 85%, but not with SRBD. In our study, we found a moderate correlation between some daytime parameters (PaO_2, FVC, and FEV1) and nocturnal oxygenation parameters. Unlike these two studies, we found that AHI correlated with FEV1 and FVC. A study with 25 MD patients showed that 12% of the patients with SRBD would have been missed if only mouth pressures, spirometry, and arterial blood gasses were employed for the assessment. In our study this rate would be 31.3%.

A number of studies have emphasized daytime hypercapnia in MD. Inspiratory muscle weakness plays an important role in the pathogenesis of daytime hypercapnia [5,9,12]. Obesity further impairs respiratory muscles [5,33]. Associated sleep apnea and impaired central respiratory drive may intensify hypercapnia. Daytime hypercapnia was a common finding in this study but there was no correlation between hypercapnia and AHI. On the other hand, hypercapnia was correlated with both FVC and FEV1, showing the effect of respiratory muscle weakness.

Published studies, in general, have shown that central apneas are more common than obstructive apneas in MD [2,3,6,16,24]. In our study, hypopneas were more common than apneas and unlike other studies, central apneas were not as common as obstructive apneas. Of the 16 patients with sleep apnea, 13 had obstructive sleep apnea. The explanation for detecting more obstructive sleep apnea may be upper airway pathologies in MD. Patients with MD usually have facial and jaw muscle weakness. Weak pharyngeal or laryngeal muscles may not be able to sufficiently stabilize the upper airway during inspiration, predisposing to airway narrowing and increased upper airway resistance [10,35,36]. As a result, increased upper airway resistance during REM sleep may contribute to obstructive hypopneas. Another explanation for predominantly reported central apneas in earlier studies may be the difficulty in the classification of events as "central" or "obstructive" in neuromuscular diseases. Obstructive apneas may be misclassified as central when respiratory muscles are too weak to move the chest against a closed pharynx [4].

This study has some disadvantages, the major ones being its retrospective nature and the absence of comparison with patients who had EDS. The absence of nocturnal carbon dioxide (CO_2) monitoring to evaluate sleep-related hypoventilation may be a weak point of this study. End-tidal CO_2 monitoring is useful in pediatric cases and transcutaneous CO_2 monitoring poorly correlates with $PaCO_2$. Neither is currently considered as a routine part of sleep assessment in adults. Also, the American Academy of Sleep Medicine Task Force consensus reported that these measurements should not be used routinely to diagnose sleep hypoventilation [37]. Another weak point is that maximum inspiratory and expiratory pressures were not used in this study. Facial muscle weakness in MD can result in underestimation of these pressures, making them unreliable. Additionally, studies in various NMD have shown that these measurements have no correlation or poor correlation with nocturnal parameters. Despite these disadvantages, the distinctive characteristic of our study is that it evaluated sleep apnea in adult MD patients who have no excessive daytime sleepiness. We also investigated the relationship between daytime parameters and sleep parameters.

In daily practice, PSG is not a routine investigation in MD patients who have no EDS, which is a strong predictor of sleep apnea. However, our study revealed that sleep apnea is very common in adult MD patients who have no excessive daytime sleepiness, even in the presence of normal daytime pulmonary function. Also, daytime pulmonary function parameters were not sufficiently reliable for screening sleep apnea. Since sleep apnea may cause an increase in morbidity and mortality by leading daytime respiratory failure, our findings show that PSG should be routine in MD patients who have no EDS and abnormal pulmonary function parameters.

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