Abstract

Objectives: Myotonic dystrophy type I (DM1) is characterized by multisystemic effects that include frequent respiratory impairment that can affect prognosis. Despite this, there are not many studies specifically evaluating such alterations and no one from Spain. The aim of this study is to evaluate respiratory impairment in a Spanish group of patients with DM1.

Materials and methods: Respiratory data were systematically collected from all patients with DM1 referred to a pulmonary clinic between June 2009 and June 2016. All patients completed the Epworth Sleepiness Scale and underwent forced spirometry test, cardiorespiratory polygraphy and blood gas analysis.

Results: 44 patients were evaluated. 21 (48%) had a ventilatory impairment. 14 (31%) had hypoxemia, 2 (4%) respiratory failure and 14 (31%) hypercapnia. 39 (87%) had obstructive sleep apnoea, 40% being severe, and 18 (40%) showed nocturnal hypoventilation. A relationship between ventilatory impairment and blood gas alterations was found. It was found a relationship between ventilatory impairment and OSA. 31 (69%) were treated with a respiratory device. Adherence was poor.

Conclusions: In this cohort of patients, the prevalence of ventilatory impairment and sleep breathing disorders were high. A careful respiratory evaluation, including assessment of sleep breathing, is advisable in patients with DM-1.

INTRODUCTION

Steinert’s disease, also known as myotonic dystrophy type 1 (DM1), is an autosomal dominant disease characterized by multisystemic effects, that include myotonia, muscular dystrophy, cardiac conduction abnormalities, cataracts, dysphagia, cognitive impairment, behavioral disturbance and endocrine disruption [1]. The respiratory function may also be affected, as a result of the weakness of the muscles involved in breathing [2]. In addition, patients with DM1 may have greater daytime sleepiness than the general population, sometimes associated with obstructive sleep apnoea (OSA) [3,4]. DM1 is the most common myotonic dystrophy in adults with prevalence around 5–20 per 100,000, but some areas, such as the Basque Country in Spain [5] or Quebec in Canada, have higher more prevalence.

The origin of the disease lies in the expansion of cytosine-thymine-guanine (CTG) triplets in the non-coding region 3 of the dystrophiamyotonica protein kinase (DMPK) gene localized in the 19q13.3 chromosome [8]. This mutation occurs sporadically during gametogenesis and is inherited in an autosomal dominant manner from one generation to another. As a result, patients suffering from DM1 have between 51 and thousands of repetitions of this triplet, while healthy individuals usually have only between 5 and 37 repetitions [9]. Although patients may have the same number of CTG repetitions and different degrees of severity of the disease, there seems to be a trend towards greater severity as the number of repetitions increases [10]. The expansion of triplets relates to the formation of RNA aggregates in the nucleus, called foci, which interfere with proteins responsible for regulating the maturation of the genetic material or splicing. The alteration of proteins that are affected by this defective maturing is partially responsible for the multisystemic effects that characterize the disease [11]. Despite frequent respiratory impairment and the fact that it can affect prognosis, there are not many studies specifically evaluating such alterations and only one from Spain [12]. That is why it seems of interest to analyze the degree of respiratory impairment in this cohort of patients with DM1 referred systematically for respiratory assessment at initial diagnosis.
Infanta Sofia University Hospital serves an estimated reference population of 300,000. Pulmonologists have worked closely with neurologists in managing adult patients with neuromuscular disorders susceptible to respiratory impairment. Patients with DM1 were referred after the first evaluation in our hospital by a neurologist, whether or not the diagnosis of DM1 had been done before in a different center. Respiratory data of all patients assessed were prospectively collected between June 2009 and June 2016. All patients underwent forced spirometry tests, cardiopulmonary polygraphy (CRP), blood gas analysis and completed the Epworth Sleepiness Scale (ESS) questionnaire with the help of the investigator. Only 18 patients underwent plethysmography. All spirometry tests were performed with the SAMRO CPFS/D spirometer and blood gases were analyzed with the Siemens Rapid Point 405. The EmblletaResmed® polygraph was used for the sleep studies. All CRP was evaluated with manual scoring. Supervised Epworth Scale was filled out for all the patients.

The following definitions were established:

- Restrictive ventilatory impairment: Forced vital capacity (FVC) below 80% of predicted, Severe restrictive ventilatory impairment: Forced vital capacity (FVC) below 50% of predicted.
- Obesità: Body mass index above 30, Obstructive sleep apnoea (OSA): Apnoea/hypopnoea index (AIH) above 5, Mild OSA: AIH 5–15, Moderate OSA: AIH 15–30, Severe OSA: AIH above 30, Suspected nocturnal hypoventilation: More than 30% sleep time with oxygen saturation below 90% (CT90%),
- Daytime sleepiness: ESS > 10
- Hypoxemia: Arterial PO2 breathing room air after 30 minutes of rest below 75 mmHg, Hypercapnia: Arterial PCO2 breathing room air after 30 minutes of rest above 45 mmHg, Respiratory failure: Arterial PO2 breathing room air after 30 minutes of rest below 60 mmHg.
- Patients received treatment with respiratory devices in the presence of OSA or nocturnal hypoventilation. CPAP treatment was prescribed to those with an apnoea-hypopnoea index (AIH) greater than 15, and BIPAP was used for those with nocturnal hypoventilation not related to OSA. CPAP and BIPAP pressures were titrated with a new CRP.

Compliance was considered inadequate when the use of the ventilation device was less than 2 hours on average, low when average use was between 2 and 4 hours, and proper when it was above 4 hours [13]. At the initial visit in neurology all patients accepted to be included in a database in order to develop research works. The IBM SPSS Statistics 20.0 software package was used for statistical data processing. Frequency tables for categorical variables and means with standard deviation for continuous variables were used for descriptive analysis. The comparison between groups was performed using 2×2 tables with the Chi-square test. The T-Student was used to compare means.

RESULTS

Forty-five adult patients with DM1 were referred and included in the study. Three patients died during the study, all of them because of respiratory failure. Twenty-five (56%) were men. No significant differences related to gender were found in ventilatory mechanics, blood gas analysis or sleep breathing (p > 0.05), but males had a higher frequency of severe OSA than women without signification (p = 0.06). Twenty-eight of the 29 patients underwent forced spirometry testing; one patient carrying a tracheostomy tube was unable to make reproducible maneuvers and was excluded. Restrictive ventilatory impairment was observed in 20 (44%), being severe in four (9%). A former smoker showed obstructive ventilatory impairment. We only had plethysmography in 18 patients. Total Lung Capacity (TLC) mean was 4144 cc ± 1536 cc and TLC% 95 ± 17. 4 patients (22%) had a TLC under 80%. Using TLC under 80% as restrictive parameter we did not find any different with using FVC. Patients were followed a mean of 42 months after the first evaluation. We had data about 28 patients with a new spirometry 2 years later after the first one. FVC mean 2 years later was 2981 ± 1038 and FVC% 83 ± 23. In 6 patients (21%) their FVC decreased a 10% and only in 1 (3%) decreased 20%. In 10 (36%) FVC was better than 2 years before. Ventilatory alterations were associated with hypoxemia and hypercapnia (p < 0.05). OSA was more frequent in patients with ventilatory impairment (p = 0.03). No relation was found between ventilatory impairment and nocturnal hypoventilation or obesity. The relationship between ventilatory impairment and respiratory parameters is shown in Table (1).

DISCUSSION

To our knowledge, this is the first reported group of Spanish patients to be referred systematically by a neurologist for assessment of respiratory impairment. As our hospital serves around 300,000 people and assuming all cases are referred, the prevalence of DM1 must be around 9 patients per 100,000, consistent with previously described [2]. Our group showed restrictive ventilatory impairment in a similar proportion to that described in the literature [2], and a high prevalence of OSA, even severe. DM1 shows an autosomal dominant inheritance and published papers have found no difference in prevalence between men and women. In our study, the same proportion of men and women were assessed and it was found no difference in the degree of disease effects of them. Kaminsky et al. [14], published...
in 2011 a retrospective study assessing the effects of DM1 in 106 patients. The proportion of men and women was similar to the one found in our study, and so was the mean age (43 years). They found that 61% of patients showed restrictive ventilatory impairment, defined as a total lung capacity (TLC) below 80% of the predicted value. We did not measure TLC in all our patients, but half of them had an FVC below 80%, four even below 50%. Only 34% of the patients studied by Kaminsky et al showed a TLC below 70%. Therefore, our data matches others in that not all patients with DM1 have a ventilatory impairment and if it is present, it is usually mild. Various hypotheses have been published attempting to explain this variability in ventilatory impairment. Some speculate that ventilatory restriction may be related to patients’ muscle strength and use the muscular disability rating scale (MDRS) to measure the severity of muscle impairment [15]. We did not ask patients to complete this questionnaire. Other studies have found a relationship between restrictive ventilatory impairment and obesity; the more obese the patient, the more likely to have a restrictive impairment [16].

In our sample, the mean body mass index was 25.4, with only 5 patients being obese, and we found no relation between obesity and ventilatory impairment. Another hypothesis suggests that restrictive impairment may be related to the number of repetitions of CTG triplets [14], but this relation was not found in other studies. Still, it seems that, as the number of repetitions increases, so does the severity of disease, including the respiratory impairment [14,17-20] Some national guidelines recommend against quantifying the number of repetitions for different reasons [21], and we did not have the number of repetitions from all patients, so we could not include this analysis. Although restrictive ventilatory impairment is not usually severe, it can cause noteworthy nocturnal hypoventilation that conditions daytime symptoms and even hypercapnia in some patients. A Canadian study on a sample of 134 patients found that 36% of them had daytime hypercapnia [15]. Patients with hypercapnia were those with worse forced vital capacity and less respiratory muscle strength measured by maximal inspiratory and expiratory pressures (MIP and MEP). In our study, mean PCO2 was normal, but similarly to the study by Bégin et al, 20% of patients showed daytime hypercapnia. Mean PO2 was also normal, 31% of patients had hypoxemia, and only 4% were in respiratory failure. As in the Canadian study, ventilatory impairment in spirometry was associated with hypoxemia and hypercapnia. On the other hand, it has been known for long that patients with DM1 report more
daytime sleepiness than the general population [22-24]. Between 40 and 80% of patients with DM1 refer excessive sleepiness during the day. Usually, sleepiness is related to OSA, but a number of studies show polysomnographic changes in sleep onset REM similar to those seen in narcolepsy [28]. This finding suggests that sleepiness in patients with DM1 may not always be due to a sleep breathing disorder. Moreover, sleepiness is sometimes difficult to differentiate from other cognitive impairments as these patients may show, or from fatigue due to muscle weakness. Excessive daytime sleepiness is shown in most studies and usually requires more complex measurements than the ESS; for instance, the Daytime Sleepiness Scale (DSS) or the Multiple Sleep Latency Test (MSLT) [26,27]. In our study, patients were only asked to complete the ESS, which showed a mean value close to 11 points, with only a half of patients scoring above 10. However, we found no connection between the ESS score and the presence of OSA or severe OSA. Previous studies also found this discrepancy. In a study of 43 patients by Laberge et al. [28], only 50% scored above 10 on the ESS, although 86% had OSA, which was severe in almost 30% of them. We assessed the presence of OSA by home CRP. We found an 87% prevalence of OSA, similar to that reported in the study by Laberge et al, and higher than that reported in the study by Picherle et al [29]. In the latter, 55% of patients had a diagnosis of OSA, which was severe in only 15%. We found a relationship between the presence of restrictive ventilatory impairment and nocturnal desaturation, and 40% of the study patients had a CT90 above 30%, suggesting nocturnal hypoventilation. Other published studies also found increased nocturnal desaturation in patients diagnosed with DM1 [25]. We also found an association between night hypoventilation and OSA with restrictive ventilatory impairment. Nevertheless, as previously mentioned, there are data supporting that factors other than sleep breathing disorders such as SOREMPs, dysregulation of REM sleep, central drive failure due to neuroendocrine disorders, restless legs syndrome or nocturnal muscle pain may be responsible for daytime sleepiness [30]. CPR is not useful in diagnosing these conditions, so it is advisable to perform polysomnography, especially in those with daytime sleepiness but without OSA, and those maintaining daytime sleepiness despite properly treated OSA. There is no clear data in the literature on when to start treatment with a ventilation device in patients with neuromuscular diseases. There is consensus on treating if the patient show daytime symptoms of hypoventilation, clear hypercapnia when awake or overnight desaturation [31], seeking to improve sleep quality, reduce daytime symptoms [32], and thus improve the quality of life [33]. However, in addition to the restrictive ventilatory impairment, most patients with DM1 also have OSA, which makes it difficult to decide whether they should be treated with CPAP or BiPAP. In our daily practice, the decision is made upon the AHI and the CT90. We treat patients with CPAP if the AHI is greater than 30, regardless of the CT90. If the CT90 is greater than 30% and the AHI is below 30 (that is, hypoventilation prevails over OSA), BiPAP is prescribed. Accordingly, almost 70% of the study patients required treatment with either CPAP or BiPAP. This proportion is clearly higher than that published in other studies, such as the one by Picherle et al. [29], in which only 30% of patients were prescribed treatment during sleep. The proportion reported by Monteiro et al. [19], was 60%, all with BiPAP, which is similar to ours. In our study, just over half of the patients who need a mechanical ventilation device were treated with CPAP and just the other half with BiPAP. Other studies report similar proportions [29]. Our patients’ tolerance to mechanical ventilation devices during sleep was generally poor; very few of them used the device, according to data derived from it, more than 4 hours per night on average. This data is similar to that from previous reports [29]. This may be related to three facts: the cognitive impairment that may occur in patients with DM1 and the coexistence of other disturbances during sleep. A subtle cognitive impairment in patients with DM1 has been described [34] and they may underestimate the importance of treatment compliance. In fact, studies that have assessed adherence to CPAP by patients with cognitive impairment or depression have reported lower compliance [35]. On the other hand, some patients may have also other sleep disorders different from OSA [30]. As a result, CPAP or BiPAP may not reduce daytime sleepiness and discourage patients to stick to treatment. At last, the face muscle weakness could be a potential factor for a proper mask adjustment, increasing leaks, and preventing correct adherence. Besides not having performed Polysomnography in assessing sleep disorders, we find two other possible limitations in our study. First, not all patients underwent plethysmography nor had their MIP and MEP assessed. We did not include MIP/MEP data because we found an enormous variability in each patient between several measures. We think it is because lack of understanding or difficulties about mouth closure. Secondly, adding a sleepiness scale different from the ESS would refine the assessment of sleepiness in these patients. In conclusion, a systematic respiratory assessment is advisable in patients diagnosed with DM1 given the high prevalence of respiratory impairment with treatment implications. This evaluation should include respiratory function tests, with total lung volume measures and arterial blood gas analysis, and respiratory sleep tests, favoring Polysomnography over CRP.

REFERENCES

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